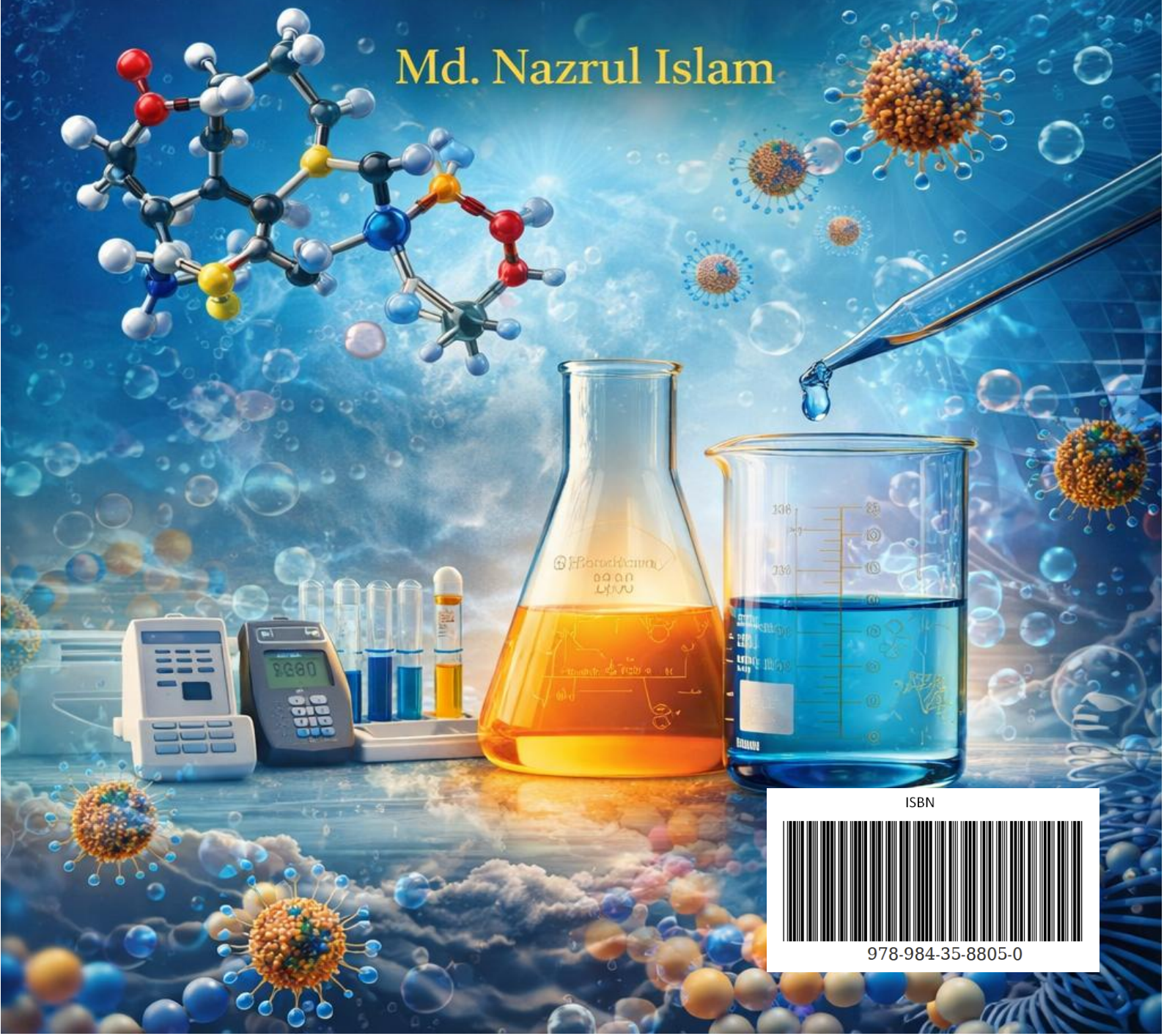
Physico-Chemical study of the Interaction of ceftriaxone sodium trihydrate antibiotic drug with surfactants in absence/presence of different additives at different temperatures

Md. Nazrul Islam



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Md. Nazrul Islam
Dhaka Residential Model College
Mirpur Road, Mohammadpur, Dhaka-1207, Bangladesh.
chemnazrul@gmail.com

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Certificate of Originality

I declare that the research work presented in this thesis entitled "**Physico-chemical study of the interaction of ceftriaxone sodium trihydrate antibiotic drug with surfactants in absence/presence of different additives at different temperatures**" submitted to the Jahangirnagar University in partial fulfillment of the requirement for the degree of Doctor of philosophy (PhD) in Chemistry is the result of the work carried out by me under the supervision of **Professor Dr. Md. Anamul Hoque** (Supervisor), Department of Chemistry, Jahangirnagar University, Savar, Dhaka-1342, Bangladesh & **Professor Dr. Shariff Enamul Kabir** (Co-Supervisor), UGC Professor, Department of Chemistry, Jagannath University, Dhaka-1100, Bangladesh.

I further declare that no part of this work has been submitted for any other degree and the work is original.

Md. Nazrul Islam

Declaration Certificate

This is to certify that the thesis submitted by **Md. Nazrul Islam** entitled "**Physico-chemical study of the interaction of ceftriaxone sodium trihydrate antibiotic drug with surfactants in absence/presence of different additives at different temperatures**" is the results of his own work. The submitted work was carried out under our supervision and guidance. The candidate has fulfilled all terms and conditions of the PhD course. We have gone through the final draft of the thesis and recommend its submission as partial fulfillment for the degree of Doctor of philosophy (PhD) in Chemistry since it is in conformity with the regulation of Jahangirnagar University and meets the accepted standard with respect to originality and quality.

Supervisor

Dr. Md. Anamul Hoque
Professor
Department of Chemistry
Jahangirnagar University
Savar, Dhaka-1342, Bangladesh

Co-Supervisor

Dr. Shariff Enamul Kabir
UGC Professor
Department of Chemistry
Jagannath University
Dhaka-1100, Bangladesh

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Dedicated
To
My Beloved Parents

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Foreword

The continuous evolution of colloid chemistry has underscored the critical importance of understanding molecular interactions in complex solution systems. Among these, the interactions between drug molecules and surfactants are of particular significance, as they directly influence drug solubility, stability, bioavailability, and transport mechanisms. A rigorous physico-chemical analysis of such systems not only advances fundamental scientific knowledge but also provides a strong foundation for practical applications in drug formulation, delivery, and therapeutic optimization.

This book offers an in-depth and methodically structured investigation into the physico-chemical interactions between the antibiotic ceftriaxone sodium trihydrate and selected cationic and nonionic surfactants. The work is distinguished by its comprehensive experimental design, systematic data analysis, and thoughtful interpretation of results within a robust thermodynamic framework. By employing conductivity measurements, cloud point analysis, and UV–Visible spectroscopic techniques, the author successfully elucidates the micellization behavior, clouding phenomena, and binding interactions that govern drug–surfactant systems under a wide range of experimental conditions.

A notable strength of this book lies in its detailed exploration of the effects of external variables such as temperature, electrolytes, hydrotropes, and polyols. These factors are shown to exert a profound influence on micellar formation, phase separation, and molecular binding, thereby highlighting the delicate balance of forces operating in amphiphilic systems. The systematic determination of critical micelle concentration, degree of ionization, counterion binding, cloud point values, and binding constants enables a clear and quantitative understanding of the underlying processes.

Equally important is the thermodynamic treatment presented throughout the book. The evaluation of Gibbs free energy, enthalpy, and entropy changes associated with micellization, clouding, and binding provides valuable insight into the spontaneity and driving forces of these phenomena. The discussion of enthalpy–entropy compensation is particularly insightful, as it reveals the relative contributions of hydrophobic interactions, electrostatic forces, ion–dipole interactions, hydrogen bonding, and π–π interactions in governing the stability and behavior of drug–surfactant assemblies.

Beyond its scientific rigor, this book holds considerable relevance for pharmaceutical and biomedical research. Surfactant micelles are frequently employed as simplified models of biological membranes, and the findings presented here offer meaningful parallels to drug–membrane interactions in vivo. The results therefore have implications not only for formulation science but also for understanding drug transport, distribution, and interaction with biological interfaces. The comprehensive nature of the study makes it a valuable reference for researchers seeking to design efficient drug delivery systems or to improve the performance of existing pharmaceutical formulations.

The organization of the book reflects a clear pedagogical intent. Fundamental concepts are introduced with clarity, experimental methodologies are described in sufficient detail to ensure reproducibility, and results are discussed in a logical and coherent manner. This structure allows the book to serve both as a reference work for experienced researchers and as an instructive

resource for postgraduate students entering the fields of physical chemistry, colloid and interface science, or pharmaceutical chemistry.

In summary, this book represents a significant contribution to the scientific literature on drug–surfactant interactions. Its careful balance of experimental precision, theoretical interpretation, and practical relevance ensures its value to a broad academic audience. It is hoped that the insights presented herein will stimulate further research and foster deeper understanding of the complex molecular phenomena that underpin modern pharmaceutical science.

Professor Dr. Md. Anamul Hoque
Department of Chemistry, Jahangirnagar University
Savar, Dhaka-1342, Bangladesh

ABBREVIATION

CTS	ceftriaxone sodium
CPC	cetylpyridinium chloride
TX-100	Triton X-100
TTAB	Tetradecyltrimethylammonium bromide
DTAB	dodecyltrimethylammonium bromide
CTAB	cetyltrimethylammonium bromide
AMT	amitriptyline hydrochloride
PMT	promethazine hydrochloride
PVP	polyvinyl pyrrolidone
CDM	cephradine monohydrate
SCAP	sodium caprylate
NaBenz	Sodium benzoate
NaSal	Sodium Salicylate
NaOAc	Sodium acetate
SDS	Sodium dodecyl sulphate
NIH	Nonionic hydrotropes
NIS	Nonionic surfactant
HDT	Hydrotrope
CFH	Ciprofloxacin hydrochloride
CLM	cefalexin monohydrate
TX-100	Triton X-100
AmCl	Ammonium Chloride
AmSul	Ammonium Sulphate
AmFSul	Ammonium Ferrous Sulphte
AmHP	Ammonium hydrogen phosphate
4-ABA	4-Amino benzoic acid
ChCl	Choline Chloride
CMC	Critical micelle concentration
α	Degree of ionization
β	Degree of counterion binding
CP	Cloud Point
K_b	Binding constant
NIS	Non ionic surfactant

Abstract

The interactions of surfactants (cetylpyridinium chloride (CPC; a cationic surfactant) and triton X-100 (TX-100; a non-ionic surfactant) with ceftriaxone sodium (CTS) antibiotic drugs were investigated by applying conductivity, cloud point and UV-Visible techniques. The effect of the concentration of all additives (salts/hydrotropes (HDTs)/polyols) on the micellization of CPC + CTS mixture at a fixed concentration of CTS and a fixed temperature (303.15K) as well as the impact of variation of the temperature on the micellization of working system at definite concentration of both CTS and additive were investigated. The micellization of CPC + CTS drug mixture has been attained to be dependent on the concentration of CTS drug, nature and concentration of employed additives as well as temperature variation. The critical micelle concentration (CMC) and degree of micelle ionization (α) of the CPC + CTS drug mixture were determined from the conductivity versus concentration of surfactant plots. In all the studied cases, only one CMC was obtained for the aggregation of the CPC + CTS mixture. The addition of CTS drug to CPC solution hampers the creation of micelle which was realized by the enhancement of CMC of CPC as a function of CTS concentration. The CMC values of CPC + CTS mixed systems were reduced (micellization was favoured) in aqueous solutions of sodium salts (NaCl and Na_2SO_4) and polyols (glucose and maltose) in comparison to water medium, while the CMC values were augmented (micellization was delayed or disfavoured) in aq. solutions of anionic HDT (sodium benzoate (BaBenz)) and polyol (galactose) media. The micellization of the CPC + CTS mixture was achieved to be happened lately by consuming a greater extent of CPC with the escalation of temperature in water and aq. solution of NaCl, Na_2SO_4, choline chloride and galactose while the earlier micellization (lesser extent of amphiphile was required for micelle development) occurred for the same working system in aq. solutions of NaBenz, ReSC, caffeine, and glycerol media. In aq. glucose and maltose solutions, the micellization was delayed at lower temperatures and favoured at higher working temperatures; while the opposite trend was found in aq. urea medium. The negative values of free energy of micellization (ΔG_m^0) indicated the spontaneous development of micelle for the CPC + CTS mixture in all media investigated. The other thermodynamic parameters (changes in enthalpy

(ΔH_m^0), entropy (ΔS_m^0) and thermodynamics of transfer for the micellization phenomena have been computed and described in detailed. The calculated ΔH_m^0 and ΔS_m^0 values of the micellization of CPC + CTS mixture indicate that the probable binding forces between CTS and CPC are ion-dipole and hydrophobic interactions. The enhanced hydrophobic interaction is recommended between the components in aq. NaBenz, glycerol and ReSC media whereas electrostatic interactions might be the dominating forces among components in aq. galactose and maltose solutions.

The cloudy creation of TX-100 was found to be delayed (the cloud point (CP) values were increased) with the introduction of the CTS drug i.e. the CTS drug enhanced the solubility of TX-100 in a water medium. The CP values of TX-100 (80 mmol kg^{-1}) + CTS (3 mmol kg^{-1}) drug mixture have been attained to be decreased (solubility was decreased) with rising concentrations of electrolytes, HDS and polyols used in the present study with a few exceptions. The increase of the concentrations of caffeine, KI, NaBenz and NaSal caused the enhancement of CP (solubility was increased) values of the working system. The cloudy creation (phase separation) process was nonspontaneous (positive ΔG_c^o) in all employed solvents media while the extent of non-spontaneity of cloudy creation was reduced with the enhancement of concentrations of salts/HDTs/polyols used. The endothermic nature of clouding was detected from the positive ΔH_c^o and ΔS_c^o values in water, and aq. solutions of NaBenz, NaSal, KI and caffeine media whereas the exothermic nature was noticed for the occurrence of phase separation in aq. solutions of employed Na/K/ammonium based salts, nonionic HDTs (resorcinol and choline chloride) and polyols (glucose, galactose and maltose) media. The negative and positive values of ΔH_c^o and ΔS_c^o were decreased as a function of respective additive concentration. The ΔH_c^o and ΔS_c^o values disclose that the recommended interactions between TX-100 and CTS drug are mainly dipole-dipole, H-bonding, and pi-pi interactions. The hydrophobic interaction is also recommended as the dominating force between the components in cases of water, and aq. solutions of NaBenz, NaSal, KI and caffeine media.

The complexation of TX-100 with CTS drug was investigated by means of UV-Visible spectroscopic method. The binding constant (K_b) of TX-100 + CTS complexation was determined from the Benesi-Hildebrand plots. The K_b were acquired to be reliant on the temperature variation. The free energy ($\Delta G_{b)}^o$ of binding was acquired to be negative

and the ΔH_b^o and ΔS_b^o values were positive. Thus the binding scheme was spontaneous, endothermic and entropy contributed phenomenon.

1. Introduction

1.1. General information of surfactants and their aggregating in solution

Surface active agents, or surfactants, are compounds that are amphiphilic in behavior and exhibit the ability to adsorb onto surfaces or interfaces of a system at low levels [1, 2]. These lead to a notable alteration of the surface or interface free energy of those surfaces. The surface tension or interfacial tension of two liquids or among a liquid and a solid can be lowered by surfactants [3]. Furthermore, surfactant contains nonpolar tail, which has little attraction to water or polar solvents (lyophobic), and polar group, which attracts water or polar solvents (lyophilic). Surfactants are classified into four categories based on the type of hydrophilic head groups. These are: Anionic, cationic, zwitterionic, and non-ionic surfactants.

Anionic: Anionic functional groups including phosphate, carboxylates, sulfate, and sulfonate are found at the head of anionic surfactants. Sodium lauryl sulfate, sodium dodecyl sulfate (such as SLS or SDS), ammonium laurayl sulfate, and the corresponding alkyl-ether sulfates such as sodium laureth sulfate (SLES) and sodium myreth sulfate are notable examples of alkyl sulfates. These are employed in textiles for dyeing and raw material preparation. These surfactants are used in shampoos, dishwashing solutions, and laundry detergents.

Cationic: These contain the surface-active part as a positive charge, such as $RN^{+}(CH_3)_3Cl^{-}$ (quarternary ammonium chloride) and $RN^{+}H_3Cl^{-}$ (salt of a long chain amine). They work well as leveling, softening, and germicidal agents as well as fungicides. The pharmaceutical and agrochemical industries make extensive use of them.

Zwitterionic: The surfactants contain both a positive and a negative charge in their structures. As for examples: $RN^{+}(CH_3)_2CH_2CH_2SO_3^{-}$ (sulfobetain) and $RN^{+}H_2CH_2COO^{-}$ (long chain amino acid).

Non-Ionic: Surfactants. having highly polar groups, such as $RCOOCH_2CHOHCH_2OH$ (monoglyceride of long chain fatty acid) and $RC_6H_4(OC_2H_4)_xOH$ (polyoxyethylented alkyl phenol) and possess no charge group, are nonionic surfactants. These work well to remove oils and grease from fabrics and metal surfaces. These are typically employed as degreasing agents, in oil recovery processes, and in mineral extraction.

Gemini surfactant is a special type of surfactant that contains more than one head and tail groups. A number of reviews address the synthesis, structure, surface active

characteristics, critical micellar concentration, and applications of gemini surfactants [4].

Interest on surfactant chemistry is ever-growing because of the extensive applications of various surfactants in industries and other sectors [5-17]. Surfactants (both hydrophobic and hydrophilic parts are present) are usable in many places, e.g., pharmaceutical research, industry of cosmetics and perfumes even as antiseptics and disinfectants, etc. [8-17]. In these circumstances, the aggregation phenomenon happens spontaneously via various forces (van der Waals forces, H-bonding, hydrophobic/electrostatic/donor–acceptor interactions) [18] and the minimum amphiphiles concentration which is required for the development of micelles (aggregates) is termed as critical micelle concentration (*CMC*) [19-26]. When any two surfactants (anionic, cationic, or nonionic) are interacted, mixed micelles are formed [27]. The existence of drug, polymer, dye, or other additives can influence the formation of micelles. The micellization also depends on the experimental environments (temperature, concentration, salts of both inorganic and organic (may hydrotrope (HDT)), solvent effect and so on [6-17, 19-22]. In these cases, the impacts of the aforementioned factors on the micellization have been analysed by the changes of *CMC*.

1.2. Cloudy development of nonionic surfactants

Non-ionic surfactants are biodegradable, less toxic, environmentally safe, and have the ability to form micelles in very dilute conditions. However, among them non-ionic surfactants have drawn significant attention to scientific community because of their extraordinary physical and chemical properties. The exceptional unique properties which make them ideally suitable to extensively utilize in different industries and other sectors. Clouding phenomena are the most common characteristic physical properties of nonionic surfactants. Solubilities of non-ionic surfactants are strongly influenced by the fluctuation of temperatures. The decreasing trend in solubility of nonionic surfactants upon the variation of external temperatures results the appearance of turbidity in solutions. The particular temperature which points out the formation of turbidity in solutions is widely known as the cloud point (CP) of surface-active constituents [28-35]. Above that critical temperature (CP), phase changes such as the transition of homogeneous phase to heterogeneous phase occur in solutions. Two

distinct liquid phases or layers usually lay out in the experimental solutions. One layer is formed with the abundance of surfactant as rich phase and other liquid layer contains less quantity of surfactant materials which is designated as surfactant-deficient phase. Due to the unequal distribution of solute species in the two distinct phases, the cloudiness is developed in the resulting solutions. For ionic surfactants the solubility in polar solvent is higher, which enhances the CP value. The presences of other ingredients affect the CP [36-38]. The detailed mechanism on the formation of cloudiness in the solutions of different nonionic surfactants compounds has yet not been clearly understood by many researchers. There still remain a persistence focus of research in regrading to various applications of surfactant materials. There are several external factors which may potentially drive surfactants solutions to turn into a mixture of two distinct layers and thus turbidity appears which led to the development of cloud points. The external factors such as temperature, concentration and additives strongly affect the clouding behaviors of various surfactants solution. It has been a major focus on understanding the effectiveness of additives on clouding so that the solutions systems could be able to display CP efficiently at their phase separation processes. The clouding properties of nonionic surfactants solutions are truly significant to utilize them as effective excipients in the pharmaceutical formulations along with drug carriers [39]. Within a particular class of the nonionic surfactant, the CP is significantly impacted by the quantity of (Ethylene Oxide) EO-units present in the molecule. The CP point rises as the quantity of EO unit does. Furthermore, it has been shown that the cloud point of a nonionic surfactant changes with its concentration [40-45].

1.3. Importance of Clouding phenomenon

Clouding, also known as phase separation, is a feature of amphiphilic medicines and surfactants that is impacted by temperature. This phenomenon is typically seen in nonionic surfactant micelle solutions when the temperature reaches a particular point [46-48]. Cloud point (CP) identification is important for the storage system. At higher temperature from CP indicates storage instability.

Also, the cloud-point method of extraction is the most important use of the concept of clouding phenomena of nonionic surfactants. These consist of the removal of environmental contaminants, the purification and separation of biomolecules, and the extraction of metal ions. The cloud-point extraction approach holds great potential as a

solvent extraction option in the future. The term "cloud point" in the petroleum sector describes the temperature below which biowax in biodiesels or diesel wax forms a hazy look.

1.4. The importance of the study of drug-surfactant interactions

It is well recognized that surfactants are essential in both basic and applied disciplines. In pharmaceutical formulations, surfactants are widely utilized as diluents, emulsifiers, disintegrating agents, and solubility enhancers [49-51]. Drug delivery and targeting systems also engage surfactant systems to diminish drug loss and degradation, avoid negative side effects, boost drug's bioavailability, and make drug acceptance easier to control [3, 46, 52]. Surfactant micelles can remain in the body (blood) for extended periods of time, allowing for progressive accumulation in the required part, because they increase the solubility of weakly water-soluble medications and therefore, upsurge their bioavailability. In this particular situation, surfactant micelles serve as drug transporters and so enhance the therapeutic efficacy of pharmaceuticals.

Within the hydrophobic portion of membrane surfaces, the majority of biological activities take place. The surface of biological cells often exhibits a net charge due to the ionized head groups of the lipids, which results in distinct binding characteristics for various charged and uncharged molecules, including medications. Additionally, the self-aggregation characteristics of the drug and its intricate interactions with the surrounding molecular environment, such as tissues and membranes, determine how well it distributes both ionic and nonionic medications throughout the body [53]. The mechanism of drug action is related to the physico-chemical interactions that pharmaceuticals have with tissues and membranes. One can picture how medications interact with surfactant micelles as a rough representation of how they interact with biological surfaces. Important details regarding the transportation of medications across cell membranes are also supplied by this. Lipids are paired with protein and glycoproteins that are to form biological membranes [54]. The most prevalent type of lipid in membranes in living things is phospholipid, which is arranged in an intricate bilayer structure. Although surfactants do not form complicated bilayer structures, they do have both hydrophobic and hydrophilic parts in their structures, similar to lipids. Therefore, surfactant micelles can be believed as a simplified model of biomembranes,

enabling researchers to inspect how various substances, including medications, interact with membranes [54-57].

1.5. Review

1.5.1. A review on the micellization of ionic surfactant

Hoque *et al.* [58] examined the micellization of cetyldimethylethylammonium bromide (CDMEAB) in the appearance of cefalexin monohydrate (CLM) using conductivity method in water and aq. solution of salts. Two critical micelle concentrations were gained for the CDMEAB and CLM + CDMEAB systems in all circumstances. The micellization of the CLM + CDMEAB system was found to be favorable in aq. solutions of KCl and K_2SO_4. The values of ΔH_m^0 and ΔS_m^0 data displayed that the hydrophobic and electrostatic binding interactions were the plausible interactions between CLM and CDMEAB.

Hoque *et al.* [59] explored the association of dodecyltrimethylammonium bromide (DTAB) in the presence of three cephalosporin drugs in water and aq. solution of K_2SO_4 salt. The experiments were performed thorough conductivity measurements. In the presence of salts, the micellization was happened favorably.

Akhtar *et al.* [60] investigated the interaction of sodium dodecyl sulfate (SDS), and cetyltrimethylammonium bromide (CTAB) with cefadroxyl monohydrate (CFM) through micelle development study using conductivity technique. In both cases, only one *CMC* has been detected. The inclusion of NaCl significantly reduces the *CMC* values for both surfactant systems, suggesting the earlier micelle creation in aq. NaCl medium than in pure water.

Kabir-ud-Din *et al.* [61] studied mixed micelle formation of gemini surfactants and amitriptyline hydrochloride (AMT) mixture in aqueous solution. The authors determined the critical micelle concentration, degree of dissociation, and excess energy of mixing.

Mata et al. [62] investigated the aggregation of cationic surfactant in water through surface tension, viscosity, electrical conductivity, and dye solubilization methods. For cationic surfactants, the critical micelle concentration, counters ion binding (β),

aggregation number, and sphere-to-rod transition are illustrated. The law of mass action model was utilized to evaluate the thermodynamic parameters.

Rub *et al.* [63] inspected the mixed micelle formation of TX-100 and promethazine hydrochloride (PMT) mixture in water environment at numerous compositions and temperatures by means of conductometric technique. The determined critical micelle concentration (*CMC*) values are less than the CMC^{id} values, indicating that the components of the mixture interact attractively. Synergistic interactions are suggested by the negative values of the interaction parameter (β) resulting from the regular solution theory (RST). The derived the activity coefficients (f_1 and f_2) from theoretical models, which were always less than unity, suggesting nonideality in all binary mixture.

1.5.2. Review of nonionic surfactant clouding phenomena

Because of the solute–solvent interaction, additions for nonionic surfactants may have a lowering or rising influence on the clouding temperature [64-65].

Bhatt *et al.* [66] examined the impact of tetraethyl ammonium tetrafluoroborate [TEA(BF_4)] ionic liquid (IL) on the CP of several nonionic surfactants. At various concentrations of IL, the thermodynamic variables of these mixtures were computed. In the majority of test cases, the CP values were augmented with IL concentrations. For every case, the standard Gibbs free energy showed a positive value, indicating that the process is not happening spontaneously.

Hoque *et al.* [67] inspected the CP measurements of TX-100 in the presence and absence of organic additives, including polyols (glycerol, glucose, fructose, and sorbitol) and diols (1, 2-ethanediol; 1, 2-propanediol, and 2, 3-butanediol). Cloud points for the diol + TX-100 system were realized to rise with the increasing concentration of diols. In polyols + TX-100 system, a rise in polyol concentrations caused a drop in CP values for the same system and a trend was followed as: $CP_{glycerol} < CP_{glucose} < CP_{fructose} < CP_{sorbitol}$. For every system under investigation, the values of ΔG^0_c were discovered to be positive. Upon clouding of TX-100, it was discovered that the values of ΔH^0_c and ΔS^0_c were positive when diols were present, but nearly negative when polyols were present.

Naqvi *et al*. [68] analyzed the phase separation of amphiphilic drugs (phenothiazines (promethazine and promazine hydrochloride) and tricyclic antidepressants (amitriptyline, imipramine, and clomipramine hydrochloride) in the appearance phospholipids. The clouding behavior varied depending on the kind drugs and composition of the phospholipids.

Hoque *et al*. [69] studied the CP measurements of Polyoxyethylene (20) sorbitan monooleate (Tween 80), in an aqueous environment and in aq. polymers (Polyvinylpyrrolidone, PVP; Polyvinyl alcohol, PVA; Polyethylene glycol, PEG) solution. They inspected the impacts of salts (sodium chloride, NaCl; sodium sulfate, Na_2SO_4; sodium nitrate, $NaNO_3$). The addition of sodium salts caused the reduction of CP values of TW-80. The cloudy creation was occurred nonspontaneously (positive values of ΔG^0_c). The ΔH^0_c and ΔS^0_c values were found to be nearly negative which indicated that the process was exothermic and controlled by enthalpy domination.

Patill *et al*. [70] measured the CP of Brij-58 tin the presence of phenylalanine (PA) and alanine (Ala). As the concentration of Brij-58 increased, the CP of pure surfactant was dropped.

Batigöc *et al*. [71] examined the CP for the TX-100 in aq. solutions and aq. solutions of gemini and conventional cationic surfactant. The temperature of the cloud point was measured using a spectrophotometer as opposed to visual observation. The CP of the TX-100 solution was increased when the cationic surfactants were added to solution of TX-100. For both gemini and conventional cationic surfactants, the standard free energy ($+\Delta G^0_c$) increased with increasing hydrophobic alkyl chain; however, it dropped with increasing surfactant concentrations.

Alauddin *et al*. [72] examined the clouding mechanism and the impact of additives on the cloud point. A significant upsurge in CP of Triton X-100 aqueous solutions is observed above the 4% concentration of TX-100. In 4 and 10% TX-100 solutions, the addition of hexane, heptane, octane, and decane caused the fall in CP. Higher chain length alkanes are more efficient in dropping the CP. Higher chain alcohols lower the CP, while lower chain alcohols promote the CP. For TX-100 solutions with the same

amount of alcohol, the order of the depression of the CP is as follows: decanol > octanol > heptanol > hexanol > butanol.

Amin *et al.* [73] reported the CP of TX-100 in attendance of antibiotic drug levofloxacin hemihydrates with additives and the results showed the dwindling of CP for a particular concentration of TX-100 with increasing in the extents of the drug species.

Hasan *et al.* [74] examined the clouding phenomena and thermodynamics behavior of metformin hydrochloride and triton X-100 mixture in attendance of different potassium salts solutions. They observed the declining of CP values of the designated mixtures with rising in the concentrations of potassium salts solutions.

Mahbub *et al.* [75] conducted a detailed study on CP in the triton X-100 solutions with aqueous and polyols media in the appearance of ciprofloxacin hydrochloride (CFH) as well as in the absence of the respective drug compound. They observed the lowering of the magnitudes of CP in the triton X-100 solutions with aqueous polyols due to the activities of ciprofloxacin hydrochloride drug [75].

1.5.3. An overview of drug-surfactant binding

The interaction of fluoroquinolone antibiotic drug namely ciprofloxacin hydrochloride (CFH) with polyvinyl pyrrolidone (PVP) was analyzed by UV visible and fluorescence spectroscopic methods by Mukta *et al.* [76] The gradual upsurge in binding constant (K_b) was reported with the growth of the MW of PVP. The K_b values were also augmented with growing experimental temperature. The CFH-PVP complexation is suggested to be happened mainly through hydrophobic interaction and the process is entropically controlled.

Hoque *et al.* [77] investigated the interaction of cephradine monohydrate (CDM) drug with surfactant using UV-Visible spectroscopy at various temperatures. The authors determined the binding constants from Benesi-Hildebrand plots. Binding between CDM and TX-100 was thermodynamically spontaneous.

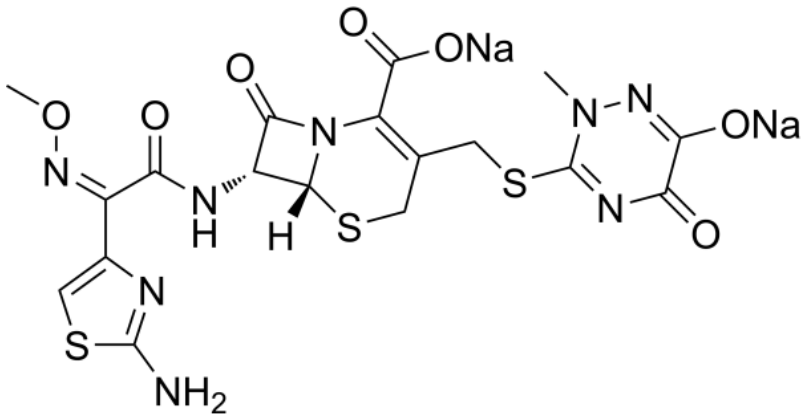
Ahmed and co-workers [34] explored the binding of TX-100 with sodium alginate (a biopolymer) in aq. EtOH /1-PrOH media using UV–visible spectroscopy. The binding

constant (K_b) was determined through Benesi-Hildebrand plot and the K_b values were obtained to be dependent on temperature and solvent composition. The study recommended the hydrophobic, hydrogen bonding, and electrostatic interactions as contributing binding forces between TX-100 and SA.

Hoque *et al.* [78] investigated the interaction of cephalexin monohydrate (CLM) with TX-100 using UV–Visible spectroscopy. The K_b values for CLM + TX-100 mixture depended on solvent composition and temperature as well as the binding was happened through electrostatic and hydrophobic interactions.

1.6. ***Drug used in the current study***

Ceftriaxone sodium salt (CTS; Scheme 1) has been selected as a drug molecule in the current study. It is a third-generation cephalosporin antibiotic drug which is used in the treatment of bacterial diseases. It showed significant pharmacological activities in vitro towards the Gram-



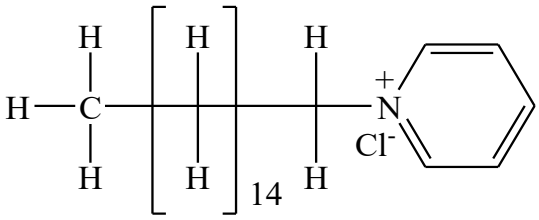
Scheme 1: Structural diagram of ceftriaxone sodium.

positive and Gram-negative bacteria. CTS exhibited a broad-spectrum of activities as a potential curative drug and has been successfully applied to treat the infected lungs, urinary tract, skin, abdomen, bone, joints, and brain as well as to stop infections such as gonorrhea and community-acquired pneumonia [79-80]. Before surgery, it is immediately injected into a patient's muscle or vein to successfully protect them from bacterial infections.

CTS is directly inserted into muscle or vein of patients before surgery that effectively prevent patients from bacterial infections. CTS drug is used to treat inflammatory diseases as well [79-82]. The CTS drug can interact with different surfactants (cationic, anionic, or non-ionic) such as tetradecyltrimethylammonium bromide (TTAB), Triton X-100 and Tween-80 at varied environmental conditions have already reported [80].

1.7. Surfactants used in the current study

In the present study, cetylpyridinium chloride (CPC) and triton X-100 (TX-100) have been chosen as cationic and nonionic surfactant in the present investigation. A quaternary ammonium salt CPC (cationic surfactant) has various usable advantages for example as reducing dental plaque, gin-givitis with the help of 0.05% CPC [83], antiviral effects in patients with influenza to shorten the period and cruelty of the virus [84-85], can scupper viral capsids [86] and can also affect enveloped viruses like coronaviruses [87]. For the quick and easy wound dressings process with a control antibacterial agents release, cetylpyridinium chloride was electrostatically immobilized to poly(vinyl alcohol) hydrogels [88].

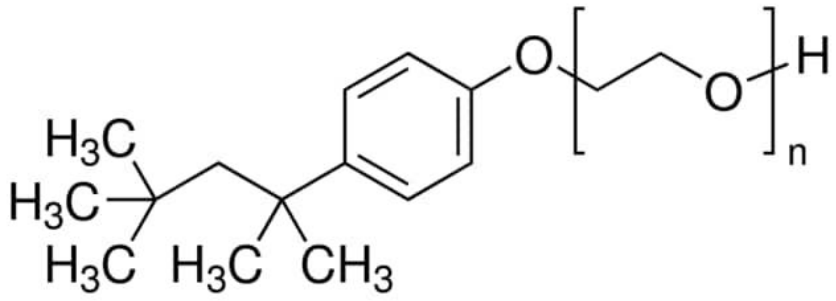


Scheme 2: Cetylpyridinium chloride

In aqueous solutions, the aggregation of sodium caprylate (SCAP) and CPC in the existence of the polymer polyvinyl pyrrolidone and different non-ionic surfactants has been also studied [89]. The polymer-surfactant interactions are crucial in terms of industrial application like pharmaceuticals, detergents, paints and coating, food as well as cosmetics. Surfactants affect emulsification capacity, colloidal stability, and interfacial tension in these mixed systems, whereas polymers offer regulation of colloidal stability and rheological features [90]. CPC also used as mouthwashes, toothpastes, lozenges, and breathe and nasal sprays.

In laboratories, polyoxyethylene surfactants are employed as emulsifiers and detergents. These are thought of as mild surfactants. Interesting structural properties of

TX-100 include the polyoxyethylene moiety at one side and an elongated chain alkyl phenyl group as a hydrophobic part at the other end of the molecules (Scheme 3). The TX-100 has been utilized to separate biomolecules, to extract membrane protein, as constituents in co-immunoprecipitation experiments and in the laboratories for washing purposes [91-92]. Furthermore, TX-100 is used as a constituent of influenza vaccinations like Fluarix, Flublok, and Fluzone, as well as a way to reduce the surface tension of an aqueous system during immunostaining and a constituent of the lysis buffer for DNA extraction [74, 93-95]. Surfactants are also hired in the production of solutions of compounds with the purpose of having synergism in numerous systems [94].



Scheme 3: Structural diagram of TX-100 (*n* = 9-10).

The pressurized liquid extraction (PLE) method has the usages to extract the pharmacologically increased active ingredient ginsenoside from ginseng roots using aqueous solutions of the NIS TX-100 [96]. Literature has also shown that the TX-100 has been utilized to compress the floating of coal particles in the reverse floatation of non-coking cool fines [97]. The crystallization rate of beta-zeolite produced by hydrothermal procedures has been effectively increased by the use of a modest amount of TX-100 [98].

1.8. Hydrotropes and their usages

HDTs are amphiphilic compounds that means they contain both polar (hydrophilic) and non-polar (hydrophobic) parts in their structures. But the hydrophobic part is short and thus cannot aggregate spontaneously like surfactant. As for example, sodium benzoate (NaBenz) is a small amphiphilic molecule which possess carboxylate part (as charged/hydrophilic nature) and phenyl group (as hydrophobic part) [99]. Due to having both hydrophilic and hydrophobic part, they are capable to solubilize the substances that are not able to be soluble in water easily or insoluble (mainly organic

compounds) [100]. The tail parts of HDT molecules are lesser (having carbon number less than 7) than the primitive surfactant molecules [101]. They can endure self-aggregates in solution that are more effective than other amphiphiles which can form self-aggregates [102-103]. Nature of self-aggregations of HDT molecules can be observed by different processes such as viscometric, tensiometric, dye-solubilisation, conductometric, UV-Visible spectrophotometric, isothermal titration calorimetry etc. and corresponding concentration is called critical minimum HDT concentration (MHC) [104-105]. HDTs represent the impact on the aggregation nature of surfactant (micellization), and other properties of surfactants. The solution behaviour of surfactants in the attendance of HDTs are published in the literature [106-107]. Detergents having HDTs (as additives) are highly effective in both aqueous and oil mediums. The possibility of transfer and proper concentration in biological fluids is restricted by their low water solubility. Adding certain hydrotropes, excipients, or biocompatible substances to improve solubility and decrease agglomeration is a common technique [108].

As a non-steroidal anti-inflammatory drug and a derivative of salicylic acid, sodium salicylate (NaSal) is used as an antibacterial, analgesic, and antipyretic [109]. In spite of this, salicylate is most frequently used in the food industry as a dietary supplement and preservative. Moreover, food contains this naturally occurring chemical [110-112].

Sodium and potassium benzoate are widely used as food preservatives that are classified by the US Food and Drug Administration of the United States as "generally regarded as safe" substances. Foods containing these compounds may contain up to 0.1% of them [113]. Sodium benzoate is used to preserve foods whose pH is acidic. Fruit purees and pulps, olives, pickles, pickled herring and mackerel, canned vegetables, beer, jams, fruit yogurts, and salads are a few examples of these kinds of cuisine [114]. Sodium benzoate is most frequently added to sauces, mayonnaise, tomato paste, margarines, fruit preserves, and carbonated drinks. Conversely, it can be found in a variety of foods in their raw form, including cinnamon, blueberries, cloves, mushrooms, and cranberries. Sodium benzoate is therefore categorized as a chemical having a wide safety profile. Moreover, it is authorized for use in medicine as buphenyl and ammonul/utephan [115-116]. Hyperammonemia and abnormalities in the urea cycle are the reasons for their use. Sodium benzoate is a great preservative, but some

research indicates it may also be used therapeutically to treat conditions like schizophrenia, major depressive disorder (MDD), autism spectrum and neurodegenerative diseases disorders (ASD) [117].

4- Amino Benzoic Acid (4-ABA) is used in the pharmaceutical sector. Commercial drugs contain its derivatives as a structural component [118]. Additionally, it can be transformed into crosslinking agents and particularly azo dyes. The 4-ABA is also utilized as a biodegradable pesticide, though its use has been limited by the development of new biopesticide variations. The 4-ABA is especially oxidized through O_2 via hydrogen abstraction as well as decarboxylation in an O_2-mediated process that promotes 4-ABA photodegradation, finds research [119].

Glycerol is a solvent, sweetener, and humectant that is present in food and beverage items. Additionally, it might help preservative, filler and thickening agent [120]. Glycerol is a tablet holding agent used in solid dosage forms such as tablets; the FDA classifies it as a caloric macronutrient among the sugar alcohols for ingestion by humans; red blood cells are preserved with glycerol in blood banks prior to their freezing; it is present in skin care products, elixirs, hair care products and expectorants, mouthwashes, toothpaste, cough syrups, soaps, allergy immunotherapies, and water-based personal lubricants [121]. Glycerol is widely utilized in pharmaceutical, medicinal, and personal care products as lubricant, a humectant, and smoothing agent. It is widely utilized in pharmaceutical formulations because to its inexpensive cost, low toxicity, and special physicochemical properties, such as water solubility and hygroscopicity [122].

Because resorcinol is a particular inhibitor of polyphenol oxidase, it can prevent browning in crustaceans that are frozen, fresh, or deep-frozen. Resorcinol makes up more than 99.5% of the major ingredient in the anti-browning agent that is expected to be approved, with citric or ascorbic acid making up less than 0.3% [123]. Caffeine can be found in coffee, tea, chocolate, and soft drinks as an addition [124-126]. Among psychoactive drugs, caffeine is the most frequently consumed one globally [126].

1.9. Aims and objectives of the investigation

It is also recognized that variations in the type and content of additives and solvents, as well as in working temperature, can affect the micellization, cloudy formation, and

binding of surfactants with drug [127-128]. An extensive review discloses that an in-depth study of the interaction of surfactants with widely used antibiotic drug is still necessary in the presence of inorganic/organic additives at variable temperatures. The interactions of CTS with surfactants (cationic and nonionic) in the presence of several additives (salts and hydrotropes (anionic and nonionic)) have therefore been examined using conductivity measurement, cloud point measurement, and UV-Visible spectroscopic techniques.

The objectives of the study are:

- To investigate the nature of aggregation of the CPC + CTS and TX-100 + CTS mixture.
- to describe how CTS drug interacts with surfactants.
- To study the effect of the composition of the salts/ hydrotropes (both anionic and nonionic) on the micellization and clouding processes of drug-surfactant mixtures.
- To explore the effect of temperature on the micellization of drug-surfactant mixture.
- to determine binding constant (K_b) of TX -100 + CTS mixture in an aqueous medium and the impact of temperature on the K_b values.

For the micellization process of CPC + CTS and TX -100 + CTS mixtures, clouding of TX -100 + CTS, and binding phenomena of TX -100 + CTS in used solvents; several physico-chemical parameters such as the *CMC*, degree of dissociation (α), CP, binding constant (K_b) and thermodynamics and enthalpy-entropy compensation variables were assessed and described in the current investigation.

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2. Experimental

2.1 Materials and equipment's

2.1.1. Information of materials used

The following materials were used in this study as received:

Name of the Material	Obtained/Collected From	Purity
Ceftriaxone Sodium Trihydrate (CTS)	Gufic Biosciences, India	89.12%
Cetylpyridinium Chloride (CPC)	Sigma Aldrich	99%
Triton X-100 (TX-100)	Merck, Germany	-
Sodium Chloride (NaCl)	Merck, Mumbai	99%
Sodium sulphate (anhydrous)(Na_2SO_4)	Merck, Mumbai	99%
Sodium Acetate (NaOAc)	Merck, Mumbai	99%
Sodium Salisylate(NaSal)	BDH, England	98%
Sodium Benzoiate (NaBenz)	BDH, England	99%
Potassium Chloride (KCl)	Merck (Mumbai, India)	≥ 99%
Potassium Phosphate (K_3PO_4)	Sigma (Aldrich, Germany)	≥ 95%
Potassium Sulphate (K_2SO_4)	Merck (Mumbai, India)	≥99%
Potassium Bromate ($KBrO_3$)	AnalaR Normapur[r] analytical reagent	99%
Potassium Iodide (KI)	B.D.H. Chemical Ltd, England	99%
Ammonium Chloride (NH_4Cl)	Chemical Reagents, China	98.5%
Ammonium Hydrogen Phosphate ($(NH_4)_2HPO_4$)	Scharlab S.L Sentmenat, SPAIN	≥99%
Ammonium Sulphate ($(NH_4)_2SO_4$)	Merck, India	99%

Ammonium Ferrous Sulphate ($(NH_4)_2SO_4.FeSO_4.6H_2O$)	B.D.H. Chemical Ltd, England	99%
Resorcinol ($C_6H_6O_2$)	BDH Laboratory Supplies Poole, England	98%
D (+) Glucose ($C_6H_{12}O_6$)	Merck kGaA, Germany	97.5-102%
Choline Chloride ($C_5H_{14}NOCl$)	Qualikems, India	98%
Caffeine ($C_8H_{10}N_4O_2$)	Merk kGaA, Germany	≥99%
Maltose ($C_{12}H_{22}O_{11}$)	Merk kGaA, Germany	≥98%
D (+) Galactose ($C_6H_{12}O_6$)	Merck, Germany	98%
p-Amino Benzoiac Acid ($C_7H_7NO_2$)	Scharlab S.L Sentmenat, SPAIN	98.5%
Glycerol ($C_3H_8O_3$)	Sigma Aldrich, Germany	99.5%
Urea (NH_2CONH_2)	Merk kGaA, 64271 Darmstadt, Germany	≥99%
Pyrrogallol ($C_3H_6O_3$)	Scientific Laboratory Supplies, England	98%

2.1.2 Equipment used

The apparatus used in this work is as follows:

i. **Conductivity Meter:** The Mettler Toledo conductivity meter (model FiveGo F3), with a temperature-compensated cell (the manufacturer provides a cell constant of 0.524 cm^{-1}), was used to test the specific conductivity of the CPC + CTS system.

ii. **Thermo stating System:** For conductivity measurement, the RM6 Lauda circulating water thermo stated bath was used to maintain the appropriate temperature for the investigating system. The cloud point of drug-surfactant

in aqueous/salt solutions was measured in the lab using a homemade constant temperature bath. An electrical stirrer and a hitter with a contact thermometer were installed in a rectangular glass vessel used as a water container.

iii. **Spectrophotometer:** The drug-surfactant binding phenomena was examined using a computer-controlled UV-visible spectrophotometer (UV-1800 PC, Shimadzu) with a thermostatic cell holder. An electrical temperature controller (Lab Tech, Smart H150-1000) with a 20–40ºC range was connected to the cell holder. The precision of the temperature controller's settings was within ±0.5ºC. UV-PC software on a computer was used to operate the spectrophotometer. For the experiment, 3 mL of square top quartz cells with a 1 cm route length were used. The Spectrophotometer's baseline was calibrated against the solvent used in each specific investigation prior to each measurement.

iv. pH meter : Meter HANNA, HI 2211 pH/ORP

v. **Electrical balance** : RADWAG, Model No. AB204-S

vi. **De-ionized water set** : BARANSTED, SYBRON Corporation

vii. **Digital Thermometer** : Range(-50+300)ºC, EU

viii. **Shaking Incubator** : Model GFL 3031, USA

Glassware Used

The following glassware's were used in the work**:**

i. **Volumetric flask** : 10, 25, 50, 100, and 250 mL volumetric flasks

ii. **Graduated pipette** : 1, 2, 5, and 10 mL graduated pipette.

iii. **Beaker** : 25, 50, 100, 250 and 500 mL beaker

iv. **Measuring cylinder** : 50 mL measuring cylinder

v. **Watch glass, pipette fillers, pipette, dropper, stirrer** etc.

2.2. Experimental techniques

2.2.1. Procedures of Conductivity measurement

In the beginning, CPC (25 mmol kg^{-1}) stock solutions were made in a variety of solvents (CTS + H_2O/CTS + H_2O + NaCl /Na_2SO_4/NaBenz media with the necessary concentration of CTS and salts). A Metler Toledo conductivity meter (model FiveGo F3) with a polycarbonate body (the cell constant of 0.524 cm^{-1} is introduced by manufacturer) was applied to test the conductivity values of the CPC + CTS solutions in the H_2O/salt + H_2O media. Following the methodology outlined in the literature, the necessary experiments were carried out [1-3]. The measurement error for the κ values was around 0.5%. 25 mL of solvent (CTS + H_2O/CTS + salt + H_2O) was added to a test tube and then the conductivity of the employed solvent displayed by the equipment was recorded first. The stock CPC solution was then slowly added into solvent under study. The values of κ were determined for every experimental run once the proper mixing and permitting enough time for temperature equilibration. The *CMC* value of the system has been detected by a noticeable breakpoint in the κ- [surfactant] plots.

In case of the examination of the effect of nonionic hydrotropes on the micellization of CPC + CTS solutions, the stock solution of CPC was prepared using specific solvent (CTS + H_2O + nonionic hydrotrope (NIH) (Galactose/Glucose/Maltose/ChCl/Resorcinol/Urea/4-ABA/Glycerol/Caffeine) media with the desired and specific concentration of CTS and NIH). Both the stock solution of CPC and solvent contained the identical concentration of CTS and NIH so that the change of the concentration of drug and NIH did not happen due to the addition of CPC stock solution to the solvent during experimental run.

To observe the effect of pH, different buffer solutions e.g. phosphate buffer, tris buffer and borax buffer were prepared for desired pH [4] and used in the current investigation. Phosphate buffer was prepared by using 0.1M KH_2PO_4 and 0.1M NaOH, Tris buffer was prepared by 0.1M tris ($C_4H_{11}NO$) and 0.2M HCl, while borax buffer was prepared by using 0.025 M borax ($Na_2B_4O_7.10H_2O$) and 0.2M HCl. The pH was measured by using HI 2211 pH/ORP Meter HANNA instruments meter. The observed pH for phosphate buffer was 6.4 and was adjusted to 6.83 by adding 0.1M NaOH, for tris buffer 7.4 and for borax buffer 9.4.

2.2.2. Approaches of clouding phenomena

Firstly, TX-100 solution in a desired solvent was prepared. To investigate the effects of different additives, solutions of the respective additives with different concentrations were prepared using appropriate solvent. Then, these aq. additives solutions were

utilized to prepare 10 mL of TX-100 solution in attendance of fixed amount of ceftriaxone sodium salt (drug) and the freshly prepared TX-100 solution was shaken and kept half an hour to attain the proper mixing and stabilization of the solution. Then the text tube containing TX-100 + drug solution in water/aq. additives media was placed in a thermostatic water bath fitted with pen type digital thermometer. The water bath was heated accordingly until to achieve the temperature close to the CP. The CP of surfactant-drug mixtures in the existence of additives was determined properly following the established procedures reported in literatures [5-8].

With the augmentation of heating, the surfactant-drug solutions were turned into cloudy. The specific temperature at which turbidity of the experimental solution appeared was recorded. However, the cloudiness was disappeared and the surfactant-drug mixtures with additives became transparent when heating was ceased from the respected mixtures. The temperatures at which the TX-100 + CTS mixtures with additives turned into clear solutions were recorded carefully. The procedure was repeated at least three times and the results were recorded to check the reproducibility. The average temperature of the appearance and disappearance of clouding in the surfactant-drug mixture with additive solution was considered as CP of the respective system.

2.2.3. UV-Visible spectroscopic technique

The UV-Visible Spectrophotometer (1800 PC, Shimadzu, Japan) was used to carry out the drug-surfactant complexation process. Drug solutions with varying drug concentrations were formulated, while TX-100 surfactant solutions (0.594 mmol kg^{-1}) were made independently. After roughly an hour of shaking the 5 mL combinations of drug and surfactant solutions with various drug and fixed concentrations of TX-100, the absorbance of the corresponding resulting solutions was determined. Using a UV-Visible Spectrophotometer (UV-1800PC, Shimadzu, Japan), absorption spectra covering the wavelength range of 200–400 nm were acquired at 293.15–308.15K. The temperature of the resulting combination will be maintained constant during the measurement of the absorbance of the drug-surfactant complex solution using a temperature controller device (Lab Tech, Smart H150-1000) equipped with a UV visible spectrophotometer. The spectrophotometer's baseline was calibrated using the

target solvent. At the maximum wavelength of the drug-surfactant system, the absorbance of the drug, surfactant, and drugs-surfactant system was measured.

2.3. Calculations

2.3.1. Micellization of CPC + CTS drug mixture

2.3.1.1. Determination of CMC

Conductivity measurement is a straightforward and simple method for figuring out the critical micelle concentration (*CMC*) of surfactant solutions. In aqueous medium, ionic surfactants split into charged species and consequently, the increase in conductivity (κ) with an increase in surfactant concentration was detected. But after development of a specific concentration of surfactant, a deviation in the increasing trend of conductivity values was obtained. So a sharp

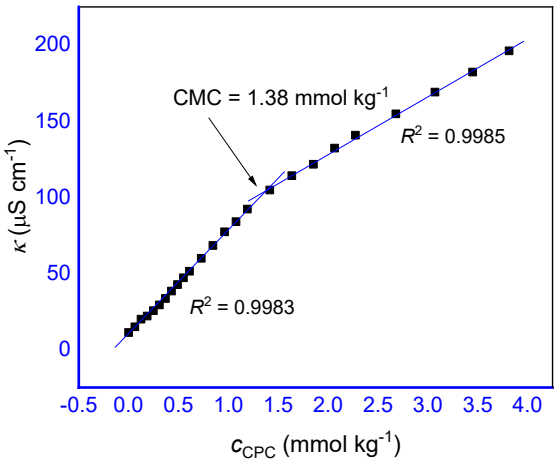

Fig. 1. Plot of *k* versus [CPC] for the aggregation of CPC + CTS in aq. Caffein (4.984 mmol kg^{-1}) at 298.15 K.

break point has been obtained in the plots of κ vs concentration of surfactant. The *CMC* of the system was determined by taking the surfactant concentration corresponding to the break point of κ versus [surfactant] plots [9-12].

2.3. 1.2. Determination of thermodynamic parameters

The different thermodynamic parameters (standard Gibb's free energy change (ΔG_m^o), change of enthalpy (ΔH_m^o) and change of entropy (ΔS_m^o)) for the micellization was determined the thermodynamic equations (2.1), (2.4), and (2.5). The feasibility of a micellization process is usually determined from the value of $-\Delta G_m^o$, here the negative ΔG_m^o value of any process indicates the spontaneous occurrence of the respective process. The ΔG_m^o of the CPS + CTS mixed system was estimated using the following equation [13-22].

$$\Delta G_m^o = (1+\beta)\, RT ln X_{CMC} \tag{2.1}$$

$$\Delta H_m^o = -(1+\beta) RT^2 \left(\frac{\partial ln X_{CMC}}{\partial T}\right) \tag{2.2}$$

Where X_{CMC}, R and T represent the mole fraction of CPC at CMC, molar gas constant, and temperature, respectively for the CPS + CTS mixed system. The plot of lnX_{CMC} versus temperature (Fig. 2) provides the quantity $\frac{\partial ln X_{CMC}}{\partial T}$ of equation (2.2).

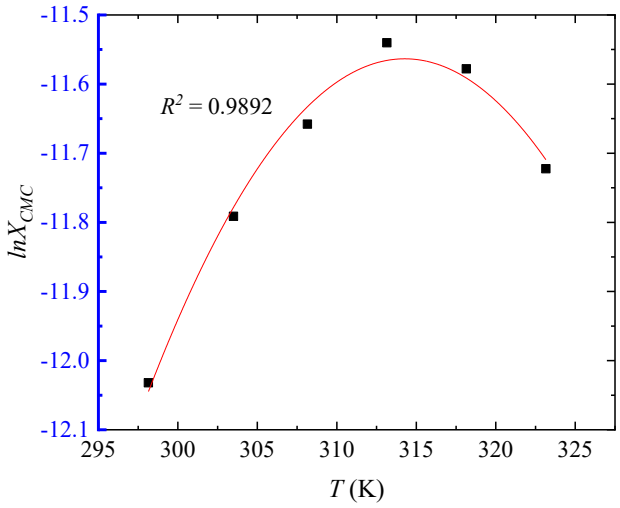

Fig. 2. A sample plot of lnX_{CMC} versus temperature for CPS + CTS mixed system in aqueous NaCl medium.

A non-linear relationship was clearly achieved from this study, which can be mathematically representable by equation (2.3).

$$lnX_{CMC} = A + BT + CT^2 \tag{2.3}$$

Here A, B and C are constants that can be obtained by regression analysis (second oder polynomial fitting). Using these achieved values of regression constants, the value of ΔH_m^o was obtained from equation (2.4).

$$\Delta H_m^o = -(1+\beta)RT^2[B + 2CT] \quad (2.4)$$

The value for ΔS_m^o was then estimated by following the thermodynamic relation given in equation (2.5).

$$\Delta S_m^o = (\Delta H_m^o - \Delta G_m^o)/T \quad (2.5)$$

2.3.1.3. Determination of Thermodynamics of transfer of CPC + CTS mixture

The changes in thermodynamics of transfer parameters, for shifting the study system from water to aq. additioves media, were estimated using the following equations (2.6)-(2.8) [23-26].

$$\Delta G_{m,tr}^o = \Delta G_m^o \text{ (aq. additive)} - \Delta G_m^o \text{ (aq.)} \quad (2.6)$$

$$\Delta H_{m,tr}^o = \Delta H_m^o \text{ (aq. additive)} - \Delta H_m^o \text{ (aq.)} \quad (2.7)$$

$$\Delta S_{m,tr}^o = \Delta S_m^o \text{ (aq. additive)} - \Delta S_m^o \text{ (aq.)} \quad (2.8)$$

2.3.1.4. Determination of enthalpy-entropy compensation parameters

The aim of studying enthalpy-entropy compensation for CPC + CTS mixture in existence of several additives is to find out the solute-solute and solute-solvent interaction present in the mixed system [23-24]. The enthalpy–entropy compensation of surfactant assembly was also detected and described by Sugihara and Hisatomi [27]. Equation (2.9) was utilized to assess the enthalpy-entropy compensation behaviour.

$$\Delta H_m^o = \Delta H_m^{o,*} + T_c\, \Delta S_m^o \quad (2.9)$$

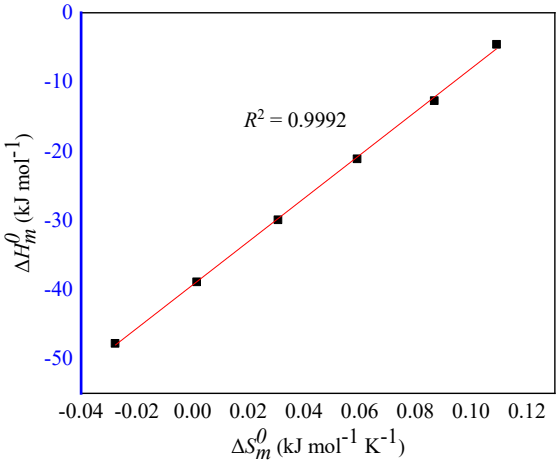

Fig. 3. The ΔH_m^0-ΔS_m^0 plot for the assembly of CPC + CTS mixture in aq. 4-ABA media.

Here, $\Delta H_m^{o,*}$ connotes the intrinsic enthalpy while T_c stands for compensation temperature. The estimated values of $\Delta H_m^{o,*}$ can reveal the solute-solute interaction, while T_c serves the purpose of identifying solute-solvent interaction. The graphical presentation for the plot of ΔH_m^o versus ΔS_m^o demonstrates a linear relationship is shown in Fig. 3.

2.3.2. Clouding phenomena of TX-100 + CTS drug mixture

2.3.2.1. Determination of CP

Cloud point measurement technique was employed to observe the clouding phenomenon of pure T X-100 or TX-100 + CTS mixture in water/ aq. additives media. The CP values of TX-100 were detected by visual inspection of the sudden appearance of turbidity or disappearance of turbidity duration of the heating/cooling of the surfactant solutions. The average of the temperatures respective to the turbidity appearance and disappearance was considered as the cloud point (CP) of the study system at a particular experimental condition.

2.3.2.2. Determination of Thermodynamic parameters of clouding

The ΔG_c^0, ΔH_c^0, and ΔS_c^0 changes for the clouding phenomena were assessed with the consideration of solubility limit at CP in the respective surfactant-drug solutions by using the following thermodynamic equations [32-36].

$$\Delta G_c^0 = -RTlnX_s \quad (2.10)$$

$$\Delta H_c^0 = RT^2\,(\partial lnX_s)/\partial T \quad (2.11)$$

$$\Delta S_c^0 = (\Delta H_c^0 - \Delta G_c^0)/T \quad (2.12)$$

where, X_s reprents mole fraction of solvated solute, R is the universal gas constant and T is the clouding temperature expressed in kelvin scale.

The development of cloud point is greatly relied on mole fraction of solute X_s, which can be stated by the following symmetric 2nd order parabolic equation (2.13) [31,37].

$$lnX_s = A + BT + CT^2 \quad (2.13)$$

where A, B, and C are the regression constants, and they can be resolved through regression assessment of least-squares. It is also mentionable that the temperature *T* is the CP of investigating system.

The enthalpy changes (ΔH_c^0) at cloud point of the TX-100 + CTS mixtures have been estimated by using the following equation (2.14):

$$\Delta H_c^0 = RT^2[B + 2CT) \quad (2.14)$$

2.3.2.3. Determination of Thermodynamics of transfer in case of clouding

The changes in thermodynamics of transfer in case of clouding was computed using equations (2.15)-(2.17) [17,23-24].

$$\Delta G_{c,tr}^o = \Delta G_c^o \text{ (aq. additive)} - \Delta G_c^o \text{(aq.)} \quad (2.15)$$

$$\Delta H_{c,tr}^o = \Delta H_c^o \text{ (aq. additive)} - \Delta H_c^o \text{(aq.)} \quad (2.16)$$

$$\Delta S_{c,tr}^o = \Delta S_c^o \text{(aq. additive)} - \Delta S_c^o \text{(aq.)} \quad (2.17)$$

2.3.2.4. Enthalpy-entropy compensation parameters of clouding

The enthalpy-entropy compensation was assessed from the linear relation in the plot of ΔH_c^0 vs. ΔS_c^0 (Fig. 4) by using the following thermodynamic equation (2.18) [38-42].

$$\Delta H_c^o = \Delta H_c^{o,*} + T_c \Delta S_c^o \quad (2.18)$$

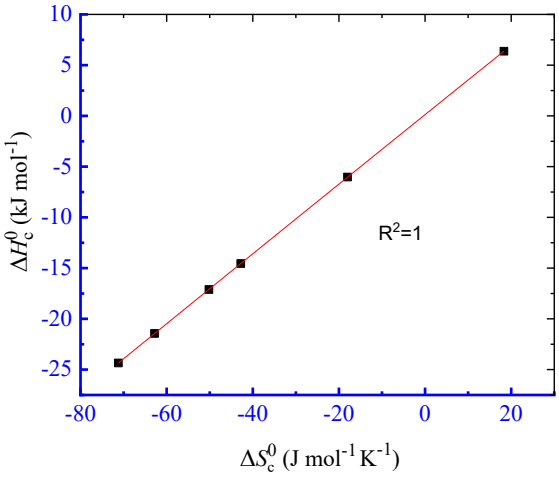

Fig. 4. The enthalpy-entropy compensation plot of clouding of aqueous mixtures of TX-100 and CTS in H_2O + Glucose.

where the slope T_c is known as compensation parameter that represents the characteristics properties of solutes and their activities in the micelle formation and ΔH_c^{o*} points out the intrinsic enthalpy gain of the system.

2.3.3. Binding study for the TX-100 + CTS drug mixture

2.3.3.1. Determination of CMC

The *CMC* was determined using a UV-visible spectroscopic technique from the plot of absorbance versus log[TX-100].

A sharp break point was acquired in the absorbance versus log[TX-100] plots and then the antilogarithm value in molar concentration was then converted to mmol kg^{-1}, and the *CMC* value was discovered. Using the UV-visible method, the determination of the *CMC* for the dye congo red + CPC and the methyl orange + CPC mixtures was reported by plotting absorbance vs. CPC concentration [43-44].

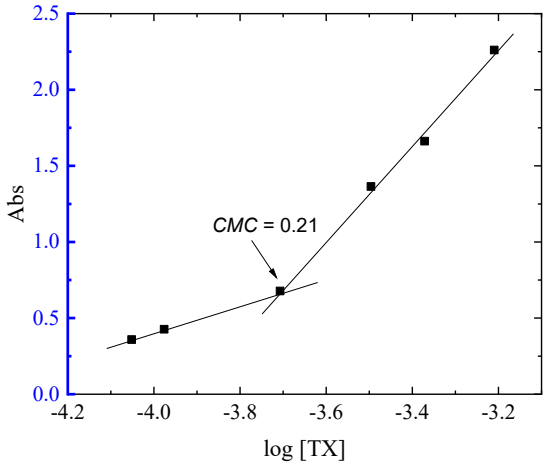

Fig. 5. The plot of Absorbance vs log [TX-100] for CTS (4.64×10^{-6} M) + TX-100 in aq. medium at 25°C.

2.3.3.2. Determination of Binding constant

The binding constant (K_b) for the drug-surfactant interaction at a definite wavelength was calculated using Benesi-Hildebrand equation.

$$\frac{[\mathrm{D}]}{\mathrm{A}} = \frac{1}{K_b \varepsilon [C]} + \frac{1}{\varepsilon} \qquad (2.19)$$

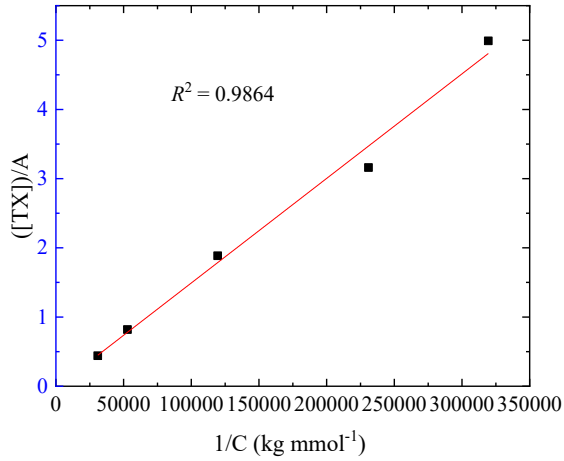

Fig. 6. Benesi-Hildebrand plot of D/A vs 1/C for CTS-TX-100 complex at 25°C

Where, the terms $[\mathrm{D}], [\mathrm{C}], \mathrm{A}, \varepsilon$ and K_b are denoted by concentration of drug, concentration of surfactant, absorbance, molar absorptivity of drug-surfactant and binding constant respectively.

From the plot of $\frac{[D]}{A} vs \frac{1}{[C]}$, the slope $of \frac{1}{K_b \varepsilon}$ and an intercept $of \frac{1}{\varepsilon}$ were found. By analyzing the slope and intercept, one can calculate the binding constant K_b. The values of binding constant from the intercept and slope can be calculated as follows.

$$slope = \frac{1}{K_b \varepsilon}$$

$$or,\ K_b = \frac{1}{slope} \times \frac{1}{\varepsilon}$$

$$= \frac{1}{slope} \times intercept$$

2.3.3.3. Determination of Thermodynamic parameters

The thermodynamic parameters such as $\Delta G^0{}_b$, $\Delta H^0{}_b$ and $\Delta S^0{}_b$ for the binding process are connected to the binding constant K_b and can be computed through the following relationship [45-48].:

$$\Delta G^0{}_b = -RT\ ln\ K_b \quad (2.20)$$

$$\Delta H^0{}_b = RT^2(\partial ln K_b) / \partial T \quad (2.21)$$

$$\Delta S^0{}_b = (\Delta H^0{}_b - \Delta G^0{}_b)/T \quad (2.22)$$

Equation (2.23) provides a symmetrical parabolic curve that represents the T dependence of K_b [45-46, 49-50].

$$\ln X_s = A + BT + CT^2 \quad (2.23)$$

Where A, B, and C are constants found by least squares regression analysis.

Fig. 7 displays a schematic parabolic curve for the plot of $\ln K_b$ versus T to calculate the regression constants (A, B and C). Then, the enthalpy change ($\Delta H^0{}_b$) of binding can be assessed by using equation (2.24):

$$\Delta H^0{}_b = RT^2\ [B + 2CT] \quad (2.24)$$

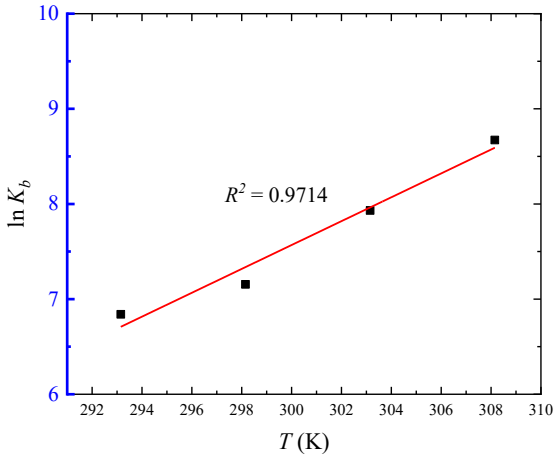

Fig. 7. Plot of lnK_b *vs* T plot for TX-100 + CTS system.

2.3.3.4. Determination of Enthalpy-entropy compensation

The enthalpy-entropy compensation in the cases of binding phenomena was assessed from the linear relation in the plot of ΔH_c^0 vs. ΔS_c^0 (Fig. 8) by using the following equation (2.25) [38-42].

$$\Delta H_b^o = \Delta H_b^{o,*} + T_c \, \Delta S_b^o \qquad (2.25)$$

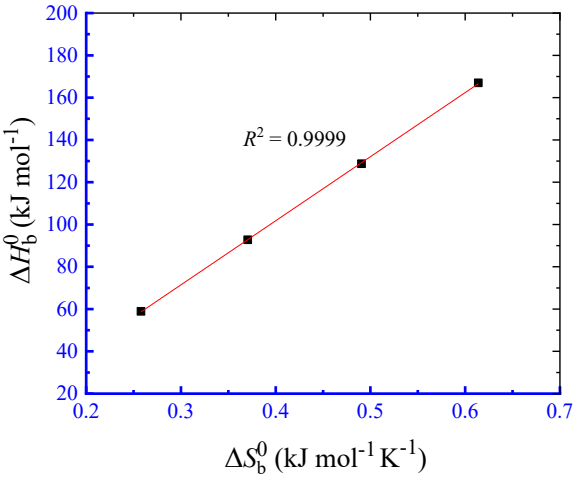

Fig. 8. Enthalpy-entropy compensation plot for the complexation of TX-100 and CTS mixed system in aqueous solution.

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3. Results and Discussion

3.1. Conductivity study of micellization

3.1.1. Evaluation of CMC, α and β for the micellization of CPC and CTS drug mixture in aqueous medium

The micellization of ionic and non-ionic surfactant is related with the changes of physico-chemical properties of the respective system [1-2]. The development of surfactant micelle can be predicted from the abrupt changes of properties like conductivity, surface tension, absorbance, density etc. [3]. In the present study, the alteration of the conductivity of CPC (cationic surfactant) + CTS drug mixture has been investigated. Information regarding the feasibility of micelle formation can be obtained by examining the *CMC*, degree of ionization (α), and counterion binding (β). The impact of changing experimental conditions (e.g., type of additive, temperature, concentration etc.) can influence the modification of micelle forming property of a surfactant. **Figure 9** shows the plot of the changes in specific conductivity of CPC + CTS system as a function of the surfactant (CPC) concentration in aqueous medium at 298.15 K. A sharp breakpoint was found in the current assessment for the whole circumstances. At low CPC concentrations, the presence of free ions (CP^+ and Cl^-) should be responsible for the initial upsurge of the conductivity. However, near the *CMC* of this mixed system, these ion starts to trap on the micellar surface, which reduces the rate of increment of the conductivity. In addition, this bulky micellar moiety is not capable to move as fast as a free ion, therefore, the conductivity of the system exhibited as less responsive with the increase of surfactant concentration. The *CMC* value of CPC + CTS mixed system, containing 0.05 mmol kg^{-1} CTS drug, was found to be 1.28 mmol kg^{-1} at 303.15 K. The reported *CMC* value of pure CPC in water is 0.90 mmol kg^{-1}, which was detected from conductivity measurement at 298.15 K [4].

The effect of concentration of CTS drug on the *CMC* values of CPC + CTS system in water medium is shown in Figure 10**.** The *CMC* values were acquired to be enhanced as a function of concentration of CTS drug. This result demonstrates that micellization is disfavourd in the presence of CTS drug and the effect has been augmented with the increase of CTS concentration in the system. Here, CTS may disrupt the hydrophobic interaction between surfactant molecules in water. This interruption may reduce the ability of CPC to form a micelle, which leads to the enhancement in *CMC* values with the growing

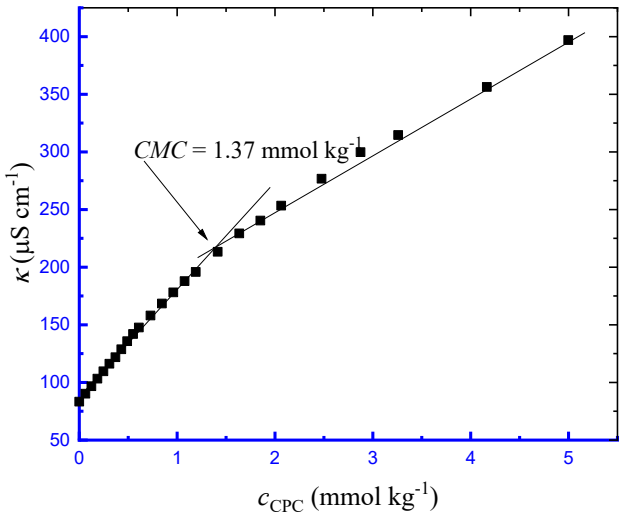

Fig. 9. Plot of κ versus [CPC] for the aggregation of CPC + CTS in aqueous medium at 298.15 K.

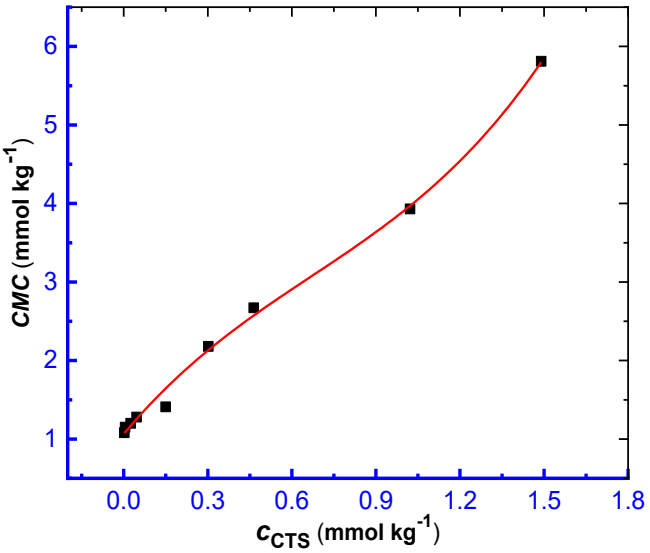

Fig. 10. The variation of *CMC* as a function of [CTS] for the aggregation of CPC + CTS in H_2O media 303.15 K.

concentration of CTS. An opposite effect has been previously observed for the cefixime trihydrate (CMT) + DTAB mixed system, where micellization of DTAB was favoured at higher concentrations of CMT [5]. The micellization is related to the value of α where a greater value represents the disfavoured micelle formation [6].

3.1.2. Effect of sodium salts and anionic hydrotrope on the micellization of CPC and CTS drug mixture

In order to detect the impacts of sodium salts on the on the micellization of CPC and CTS drug mixture, two sodium salts such NaCl and Na_2SO_4 were chosen. Also, NaBenz was selected as an anionic hydrotrope (HDT) to find its effet on the association of study system. The electrolytes used are capable to modify the properties of the solvent. The effect of concentration of electrolytes and hydrophobic salt on the CPC + CTS mixed system has been represented in Figure 11. At 298.15 K temperature, the micellization was favourable for the simple electrolytes (NaCl and Na_2SO_4), as lower *CMC* was observed. Here, with the increase of NaCl salt concetration, the *CMC* value firstly declined by a small amount and then starts to increase. On the otherhand, Na_2SO_4 always showed a slightly decreasing trend. However, *CMC* was boosted up as the concentration of NaBenz increased in the system and therefore, the formation of micelle disfavoured for the HDT (NaBenz). This result indicates that *CMC* isdependent on the concentration and properties of additives used. The addition of electrolyte (NaCl and Na_2SO_4) into the system usually stimulates the salting out process and this may increase the interaction among the hydrophobic part,

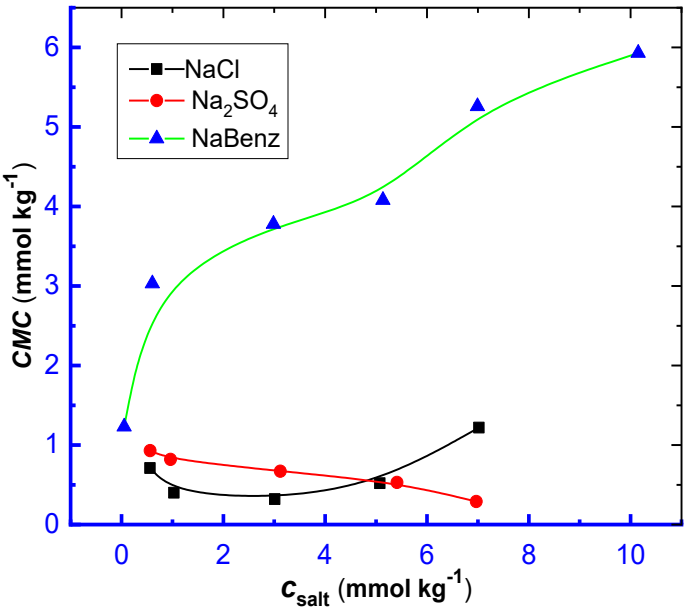

Figure 11. The variation of *CMC* as a function of [salt] or [HDT] for the aggregation of CPC + CTS mixture at 303.15 K.

which is the potential to modify the formation of the micelle [7]. In this process, the electrolyte can pull out the opposite pole of the water molecule from the micellar surface. On the other hand, the HDT (NaBenz) usually acts as a solubilizing agent, which at a lower concentration increases the ionic interactions, but at a higher concentration stimulates the molecular aggregation [8]. However, both of these impacts can disfavour the formation of micelle (i.e. the *CMC* values are enhanced).

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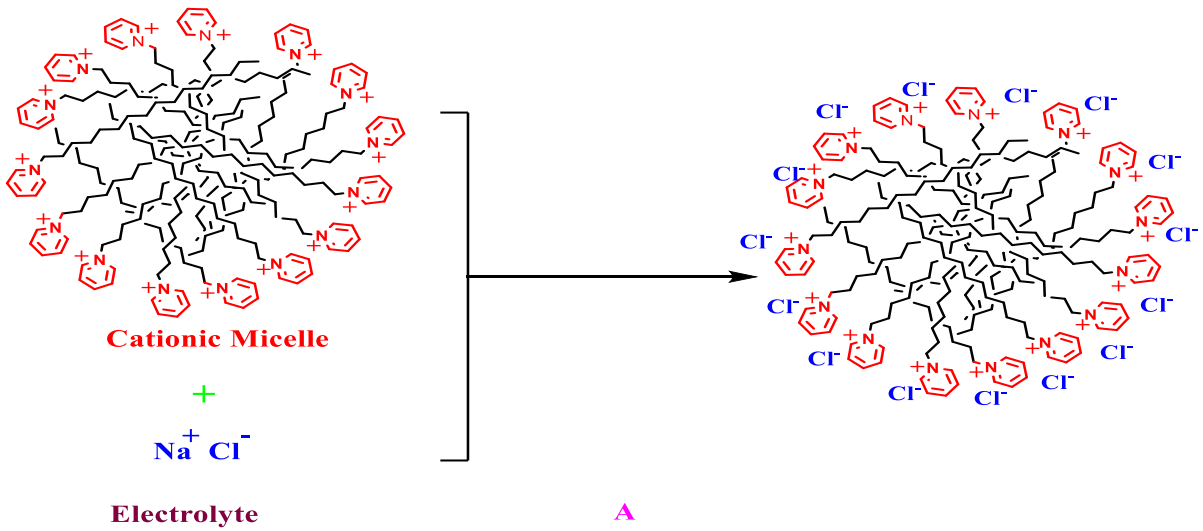


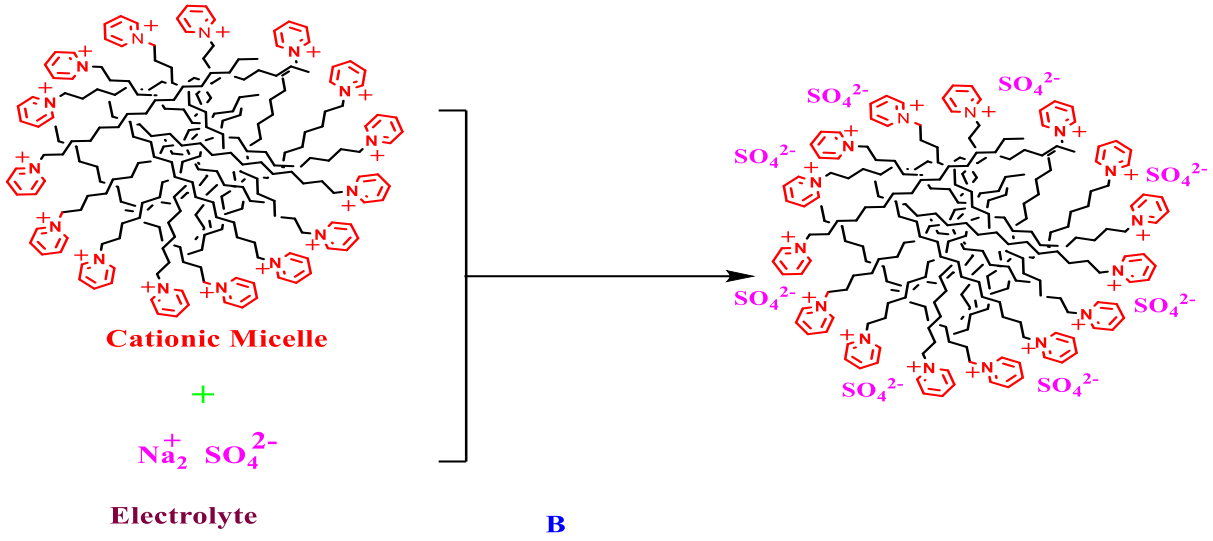
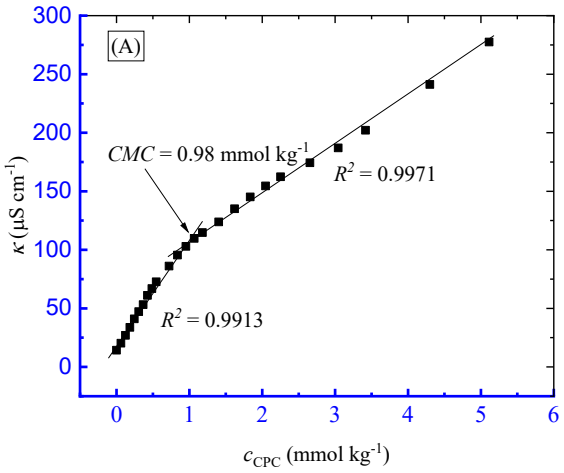


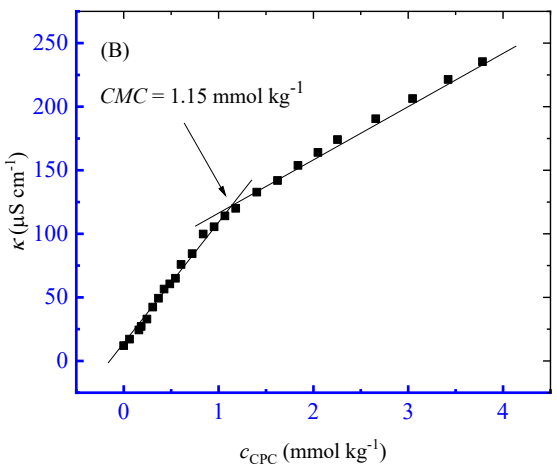
Fig. 12. The effect of electrolytes sodium chloride and sodium sulphate (A and B) on the micelle charge neutralization.

The anionic part, (Cl^-, SO_4^{2-} and benzoate) of the electyrolytes used, play a significant role in the micellization phenomenon, as all the three salts contain the same sodium ion as cation. The anions of employed electrolytes can reduce the surface charge of the micelle. A schematic diagram for the mechanism of reducing surface charge of micelle is viewed in Figure 12. This surface charge screening can clarify the relative impact on the *CMC* of CPC + CTS mixed system. In this examination, obtained results demonstrate that SO_4^{2-} ion favours the micellization more than Cl^- ion at higher concentration of respective electrolytes. This is expected due to the large size and charge of SO_4^{2-} ion compared to Cl^- ion. A similar impact has been seen earlier for the DTAB surfactant, where micellization was favoured for the Na_2SO_4 and Na_3PO_4 over NaBr electrolyte [9]. Varade et al. [10] showed the effect of Cl^- and Br^- ion on the micellization of CPC surfactant in an aqueous system. They found that Cl^- is more hydrated and less effective than Br^- ion to neutralize the ionic character of micellar surfaces. The α value at 298.15 K temperature was the lowest for Na_2SO_4 (0.15), while it was the maximum for NaBenz (0.62) added system. The α values were increased with increase in temperature from 298.15 to 323.15 K. A fluctuation was observed for the Na_2SO_4 salt, where initially the value varied without any specific trend but eventually goes in the increasing direction.

3.1.3. Effect of nonionic hydrotropes on the micellization of CPC and CTS drug mixture

For investigating the effect of nonionic hydrotropes (NIHDT) on the aggregation of employed mixture, several substances such as resorcinol, D (+) glucose, choline chloride, caffeine, maltose, D (+) galactose, p-amino benzoic acid, glycerol, urea and pyrogallol were used as NIHDT in the current investigation. The plots of specific conductivity vs. surfactant (CPC) concentration in the presence of employed NIHDTs at 303.15 K are displayed in Figures 13**.** The changes of *CMC* of the CPC + CTS system with respect to the concentration of hydrotropes are shown in Figures 14. The decrease of *CMC* was achieved in aq. solutions of glucose, galactose, choline chloride and glycerol; the effect has been found to be effective with the upsurge of concentrations of respective NIHDTs (i.e., the micellization is achieved to be happened earlier). The upsurge of *CMC* values was detected in aq. solutions of 4-ABA and resorcinol and the effect showed an increasing trend with rising respective solutes concentrations (i.e., the micellization is delayed). The *CMC* values of study system, in aq. caffeine and maltose solutions, initially declined, reached a minimal value and then increased as their concentrations undergo an increase. In case of aq. urea medium, the opposite trend of aq. caffeine and maltose solutions was acquired. The literature description demonstrated that the *CMC* values for the association of amitriptyline hydrochloride and 1-hexadecyl-3-methylimidazolium chloride mixture in urea solution were higher in magnitudes compared to those in aqueous medium; while in aq. glucose medium, the





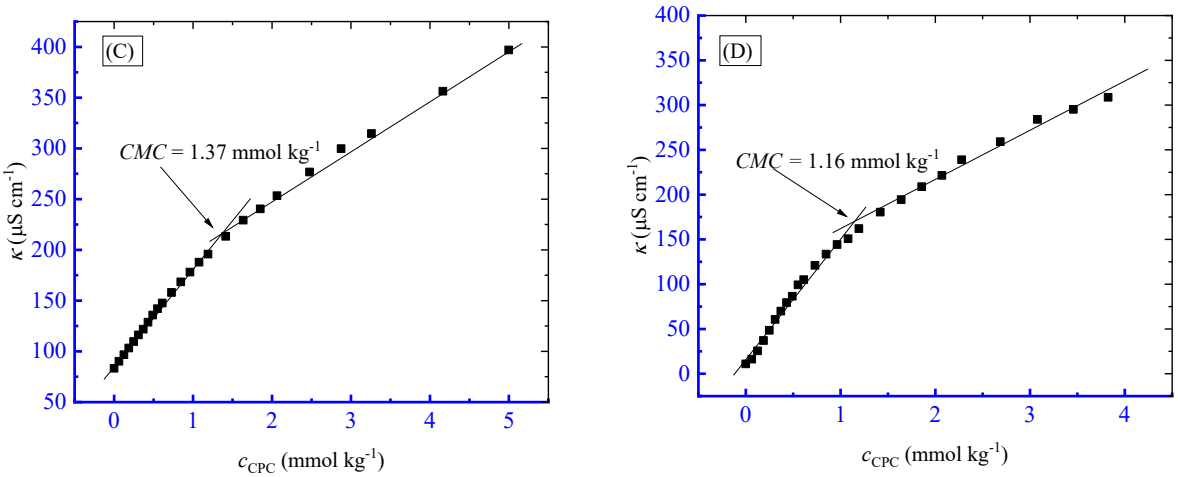


Fig. 13. The variation of κ as a function of [CPC] for the aggregation of CPC + CTS mixture in aq. (A) Glucose (399.24 mmol kg^{-1}), (B) Maltose (19.89 mmol kg^{-1}), (C) 4-ABA (5.01 mmol kg^{-1}) and (D) Caffein (10.27 mmol kg^{-1}) solutions.

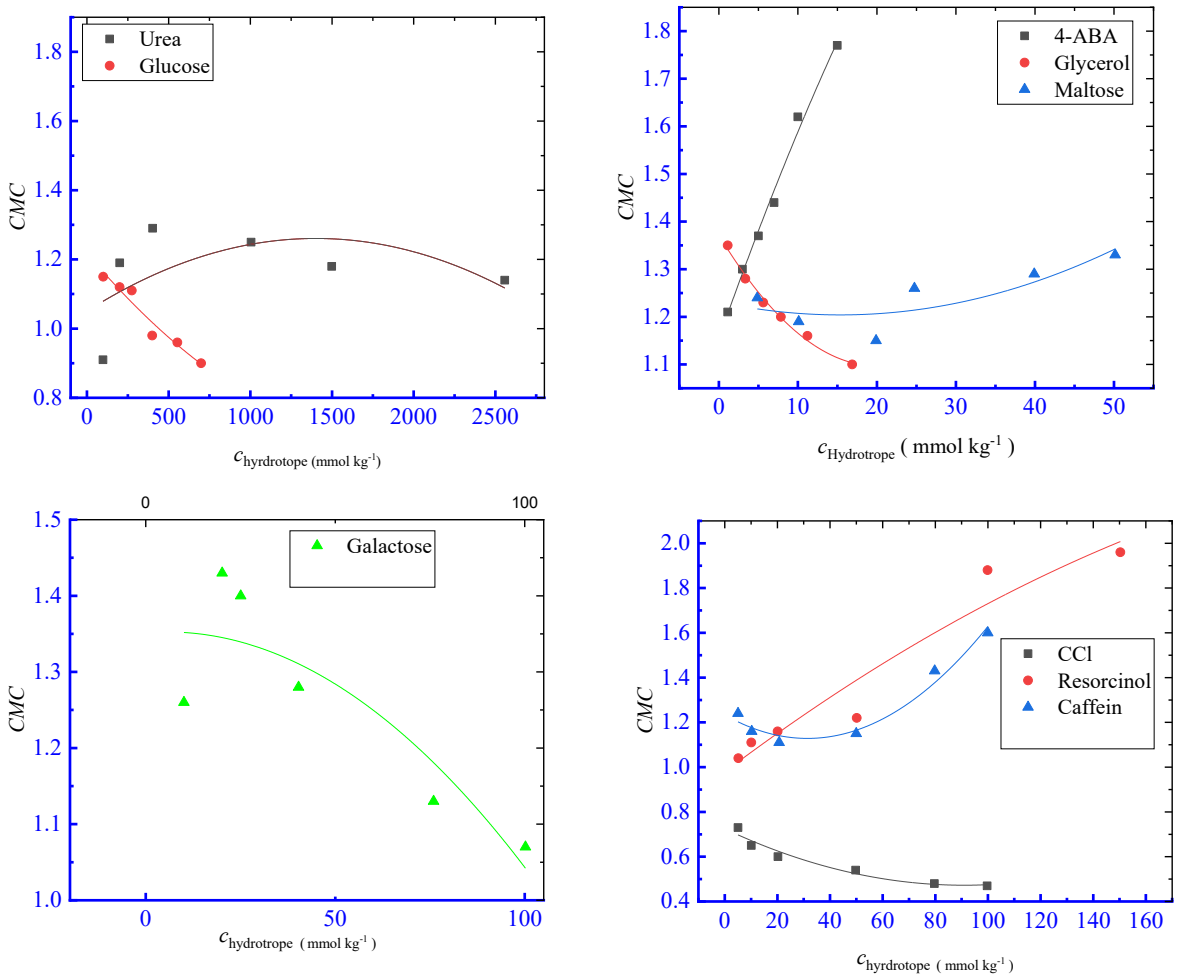


Fig. 14. The variation of *CMC* as a function of [NIH] for the aggregation of CPC + CTS.

CMC values were reported to be lower compared to those found in water environment [11]. For the association of mixed surfactants (cetyltrimethylammonium bromide (CTAB) and CPC), the *CMC* values have been reported to be decreased in the appearance of urea and resorcinol; the findings were described by Olaseni Segun Esan et al. [12]. The arrangement of the H_2O molecule around amphiphile moieties is the correct cause for the temperature change in *CMC* values. In that instance, hydrophilic hydration occurs when water is grouped with a head group; hydrophobic hydration occurs when water is arranged with an amphiphile's nonpolar tail [13].

3.1.4. Effect of temperature on the micellization

3.1.4.1. The micellization of CPC and CTS drug mixture in in aqueous and aq. Na-salts media at variable temperatures

To realize the influence of temperature on the aggregation property of employed system, a range of temperature (298.15 to 323.15 K) with a 5 K interval was selected. In this case, a definite ionic strength of electrolyte/ HDT was chosen for each medium to investigate the effect temperature. The relation of conducitivity with respect to the concentration of surfactant (CPC) at various temperatures is shown in Figure 15. Here, the specific conductivity of CPC + CTS mixture in presence of electrolyes /Nabenz increases with the escalation of temperature. Na_2SO_4 solution, the *CMC* values showed the opposite trend in comparison to aqueous and aq. NaCl media. Most interestingly, the *CMC* values in NaBenz medium are higher in magnitudes compared to aqueous and aq. NaCl/ Na_2SO_4 solutions while the *CMC* values decrease gradually with the rise of temperature. This result identifies that temperature is a dominant parameter that can modify the micellization process. The results obtained for the temperature effect on the different micellar parameters of CPC + CTS mixed system are shown in Table 1. In aqueous and aq. NaCl media, the *CMC* values firstly increase, reach a maximum value and then the *CMC* values decrease with an increase of temperature (Figure 16). The justification for the modification of micellization due to the rise of temperature is jointly responsible for two opposing factors. Firstly, the destruction of the hydration shell nearby the hydrophilic part of CPC surfactant at a higher hydrophilic hydration, which enhances the hydrophobic nature; micellization is delayed when *CMC* is enhanced by hydrophobic hydration,

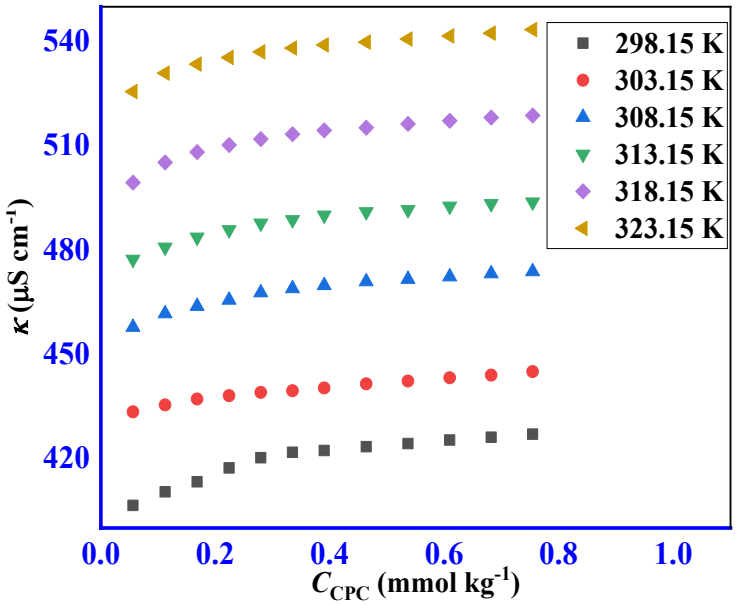


Fig. 15. Plot of κ versus [CPC] for the aggregation of CPC + CTS in aq. Na_2SO_4 (1.67 mmol kg^{-1}) at numerous study temperatures.

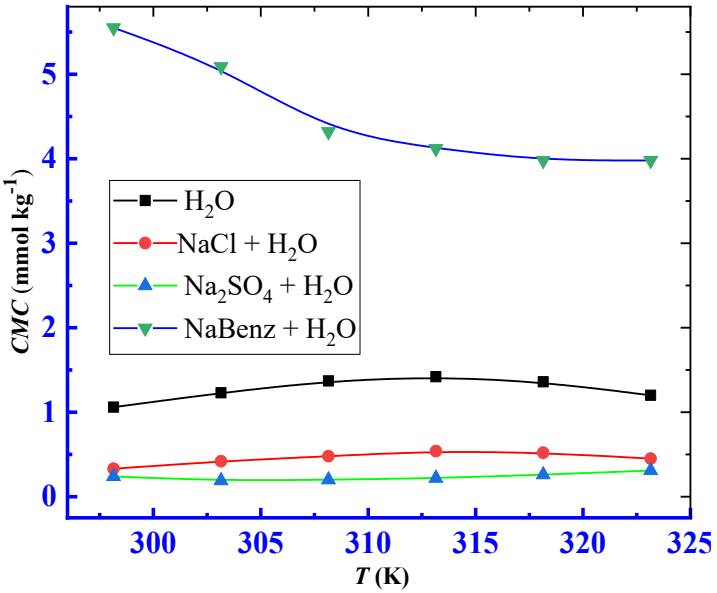


Fig. 16. The changes of *CMC* of CPC + CTS as a function of temperature in study media.

temperature favours the formation of a micelle [14]. Secondly, the disruption of the water structure around the hydrophobic part at a higher temperature has the ability to disfavour the micellization process [10, 15]. Although monomeric surfactants can undergo both types of hydrations, only hydrophilic hydration is possible once they have taken on a micellized form. In all cases, as the temperature rises, the quantity of hydration drops. Micellarization is more advantageous when *CMC* is decreased by

which encourages thermal solubility of non-polar chain [16-21]. In addition, the richer thermal movements of surfactants and water bodies make the formation of structured assemblies more difficult at higher temperatures. Since orderly assemblies are destroyed by rising temperatures, the *CMC* rises, increasing kinetic energy [22]. *CMC* levels of ionic surfactants frequently decrease as temperature rises [23]. However, depending on the surfactant, research in the literature show that *CMC* either continuously increases or continuously decreases with temperature [24-26].

Table 1. The micellar parameters for the association of CPC + CTS mixture in study media at several temperatures.

Medium	*T*	X_{CMC} ($\times 10^5$)	*A*	*β*
	K			
H_2O	298.15	1.910	0.37	0.63
	303.15	2.216	0.42	0.58
	308.15	2.469	0.42	0.58
	313.15	2.559	0.45	0.55
	318.15	2.451	0.45	0.55
	323.15	2.162	0.57	0.43
$NaCl + H_2O$	298.15	0.595	0.38	0.62
	303.15	0.757	0.44	0.56
	308.15	0.865	0.46	0.54
	313.15	0.973	0.53	0.47
	318.15	0.937	0.53	0.47
	323.15	0.811	0.53	0.47
$Na_2SO_4 + H_2O$	298.15	0.432	0.15	0.85
	303.15	0.342	0.23	0.77
	308.15	0.360	0.16	0.84
	313.15	0.396	0.22	0.78
	318.15	0.469	0.17	0.83
	323.15	0.559	0.34	0.66
$NaBenz + H_2O$	298.15	11.51	0.62	0.38
	303.15	9.999	0.60	0.40
	308.15	9.171	0.60	0.40
	313.15	7.783	0.59	0.41
	318.15	7.423	0.62	0.38
	323.15	7.171	0.65	0.35

In this study, the result indicate that, the first factor becomes dominating over the second one for the micellization of study system in aqueous and aq. NaCl (at higher

temperatures); aq. Na_2SO_4 solution (at lower temperatures) and over the whole range of working temperatures in aq. NaBenz solution. On the otherhand, second factor becomes dominating over the first one for the micellization of CPC + CTS mixed system in aqueous and aq. NaCl at lower temperatures while the similar behaviour is obtained in case of aq. Na_2SO_4 solution at higher temperatures.

3.1.4.2. Impact of temperature on the micellization of CPC and CTS drug mixture in in aq. nonionic hydrotropes media

The impacts of temperature on the conductivity and *CMC* of CPC and CTS drug mixture in in aq. nonionic hydrotropes media are demonstrated in Table 2 and Figure 17. In case of urea and ChCl, the *CMC* values initially decreased, and finally increased with increasing temperature. In aq. solutions of glucose, maltose and caffein solutions, the plots of *CMC* vs T shows inverse U- shaped behaviour. In aq. caffein, 4-ABA, glycerol and resorsinol solutions, the *CMC* values are gradually decreased as a function of temperature while the reverse trend was achieved in case of galactose solution. The change in the mode of hydration around the surfactant monomers and the drug-mediated CPC micelles can account for the fluctuation in the values of *CMC* with temperature. In the monomeric form of surfactant, both hydrophilic and hydrophobic hydrations are conceivable, whereas just

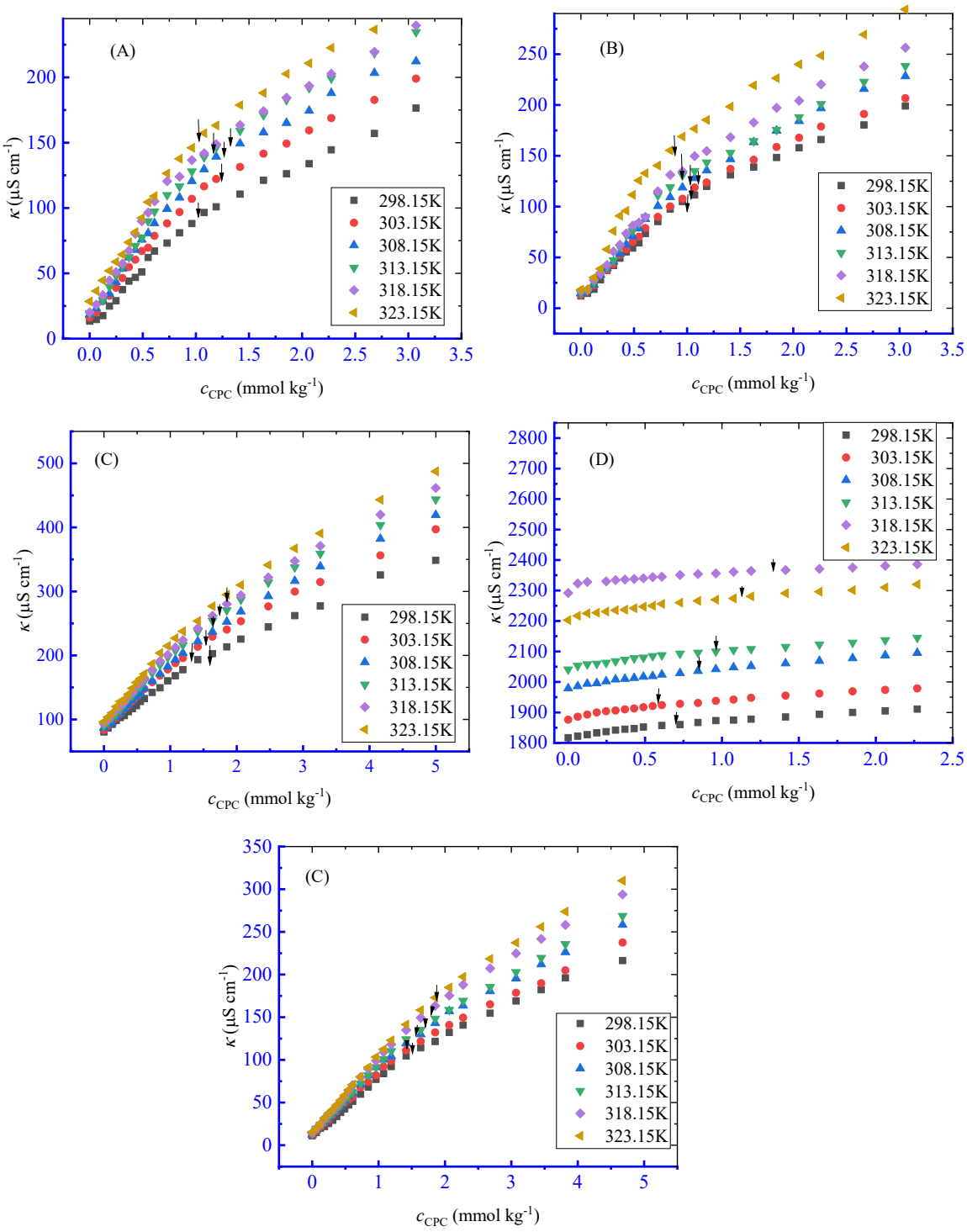


Fig. 17. Plot of κ versus [CPC] for the aggregation of CPC + CTS in aq. (A) Glucose (199.93 mmol kg^{-1}), (B) Maltose (19.89 mmol kg^{-1}), (C) 4-ABA (4.98 mmol kg^{-1}) and (D) Choline Chloride (29.61 mmol kg^{-1}) and (E) Caffein (4.984 mmol kg^{-1}) solutions at working temperatures.

Table 2. The micellar parameters (X_{CMC}, α and β) for the association of CPC + CTS mixture in aq. Nonionic hydrotropes media at several temperatures.

T	T	X_{CMC} ($\times 10^5$)	A	B
	K			
Urea+water	298.15	2.630	0.55	0.45
	303.15	2.684	0.47	0.53
	308.15	2.397	0.44	0.56
	313.15	2.254	0.53	0.47
	318.15	2.111	0.54	0.46
	323.15	1.950	0.55	0.45
Glycerol+water	298.15	2.180	0.42	0.58
	303.15	2.234	0.45	0.55
	308.15	1.946	0.36	0.64
	313.15	1.748	0.32	0.68
	318.15	1.477	0.31	0.69
	323.15	1.315	0.31	0.69
4-ABA+water	298.15	2.865	0.57	0.43
	303.15	2.685	0.53	0.47
	308.15	2.739	0.54	0.46
	313.15	2.847	0.55	0.45
	318.15	3.027	0.57	0.43
	323.15	3.315	0.6	0.4
Glucose+water	298.15	1.812	0.53	0.47
	303.15	2.099	0.36	0.64
	308.15	2.224	0.33	0.67
	313.15	2.260	0.35	0.65
	318.15	2.153	0.36	0.64
	323.15	1.991	0.37	0.63

Table 2.(Continued).

T	T / K	X_{CMC} ($\times 10^5$)	A	B
Galactose+water	298.15	1.658	0.43	0.57
	303.15	1.712	0.40	0.60
	308.15	1.856	0.39	0.61
	313.15	2.108	0.37	0.63
	318.15	2.378	0.40	0.60
	323.15	2.486	0.40	0.60
Maltose+water	298.15	1.873	0.39	0.61
	303.15	2.017	0.42	0.58
	308.15	2.090	0.41	0.59
	313.15	2.017	0.40	0.60
	318.15	1.891	0.38	0.62
	323.15	1.657	0.28	0.72
CholinCl+water	298.15	1.225	0.44	0.56
	303.15	1.207	0.43	0.57
	308.15	1.550	0.54	0.46
	313.15	1.784	0.51	0.49
	318.15	2.036	0.53	0.47
	323.15	2.396	0.50	0.50
Resorsinol+water	298.15	1.387	0.24	0.76
	303.15	1.351	0.28	0.72
	308.15	1.315	0.33	0.67
	313.15	1.225	0.39	0.61
	318.15	1.189	0.45	0.55
	323.15	1.081	0.51	0.49
Caffeine+water	298.15	2.486	0.55	0.45
	303.15	2.523	0.52	0.48
	308.15	2.504	0.55	0.45
	313.15	2.450	0.57	0.43
	318.15	2.378	0.59	0.41
	323.15	2.306	0.63	0.37

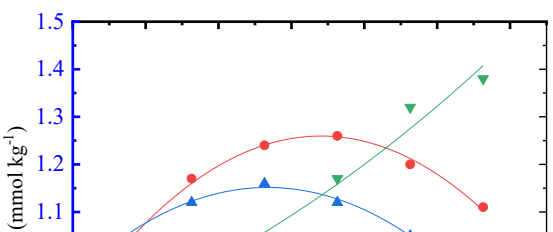


Fig. 18. The changes of *CMC* of CPC + CTS as a function of temperature in aq. (a) Glucose (248.5 mmol kg^{-1}), (b) Maltose (20 mmol kg^{-1}) and (c) galactose (25.02 mmol kg^{-1}) solution.

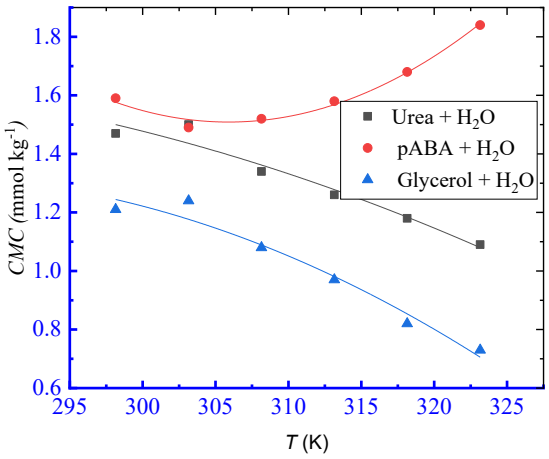


Fig. 19. The changes of *CMC* of CPC + CTS as a function of temperature in aq. (a) urea (399.1 mmol kg^{-1}), (b) 4-ABA (4.983 mmol kg^{-1}) and (c) glycerol (5.499 mmol kg^{-1}) solutions.

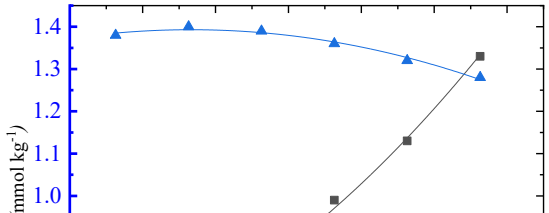


Fig. 20. The changes of *CMC* of CPC + CTS as a function of temperature in aq. (a) Choline Chloride (29.61 mmol kg^{-1}), (b) resorcinol (20.10 mmol kg^{-1}) and (c) Caffein (4.984 mmol kg^{-1}) solutions.

hydrophilic hydration is achievable for micellized CPC. With rising temperatures, a decline in both forms of hydration is anticipated. Micelle creation is more favorable when hydrophilic hydration is decreasing, and becomes disfavorable when hydrophobic dehydration is decreased as the rise of temperature happened [17, 27-29]. Thus, over a given temperature range, the extent of these two components determines whether the *CMC* values grow or decrease.

3.1.5. The effect of pH on the micellization of CPC and CTS drug mixture

The pH of the human body varies depending on the organ of the body. The control release of drug at the target point is therefore dependent on the pH. Again, the pH of the medium can alter the *CMC* of the surfactant which has been utilized as excipient in the formulation of drug. As the maximum solubilization and activity of drug is obtained at the *CMC* of the surfactant [30], the estimation of *CMC* at different pH is important. Moreover, the degradation of drug is dependent on the pH of the medium [31]. From the important point of view, we have studied the effect of pH on the aggregation of CPC + CTS mixture. The micellar parameters for CPC + CTS mixture in different buffur media at 303.15 K temperature have been provided in Table 3. The lower values of *CMC* of sodium dodecyl sulfate (SDS) as compared to aqueous medium was reported in phosphate buffer by Fuguet *et al.* [32]. Again, Ren studied the dependency of *CMC* of surfactant on pH [33]. In our study, we observed the reduction of *CMC* of CPC +

CTS mixture from aqueous to phosphate buffer (Table 3) which is in well agreement with the result of Fuguet *et al.* [32]. Again, the *CMC* values of CPC + CTS mixture was compared in different buffer media and observed that *CMC* values in borax buffer (pH of 9.4) is higher than tris buffer (pH of 4.4) which in turn higher than that in phosphate buffer (pH of 6.83) (Table 3).

Table 3. The micellar parameters for CPC + CTS mixture in different buffur media at 303.15 K temperature.

Medium	*pH*	*CMC*	*α*	*B*
		mmol kg^{-1}		
H_2O	6.95	1.23	0.37	0.63
Phosphate buffer	6.83	0.53	0.36	0.64
Tris buffer	7.40	0.77	0.37	0.63
Borax buffer	9.40	0.92	0.54	0.46

3.1.6. Thermodynamics of micellization

3.1.6.1. Thermodynamic parameters of CPC + CTS mixture in aqueous and aq. Na-salts media

To understand the interaction forces and spontaneity of the aggregation of CPC + CTS mixture in presence of additive salt, the energetics of the micellization process was characterized. All the thermodynamic parameters were analysed using thermodynamic equations as provided in the experimental section. For the calculation of enthalpy, the A, B and C regression constants (Table 4) were obtaned from lnX_{CMC} versus T plots (as for example-Figure 21).

The values of $\Delta G_{m,}^{o}$ ΔH_m^o and ΔS_m^o for CPC + CTS mixture are given in **Table 5.** The negative values of ΔG_m^o were obtained in all the electrolytes and HDT media, which indicates that the micellization in all studied media were spontaneous. The ΔG_m^o for aqueous and NaCl medium was found -43.90 and -48.32 kJ mol^{-1}, respectively, at 298.15 K (Table 5). The more negative value of ΔG_m^o in aq.Na_2SO_4 medium represent a more feasible micellization process than aq. NaCl medium, which in turn more feasible compared to aq. medium. However, the lowest value of ΔG_m^o were obtained for

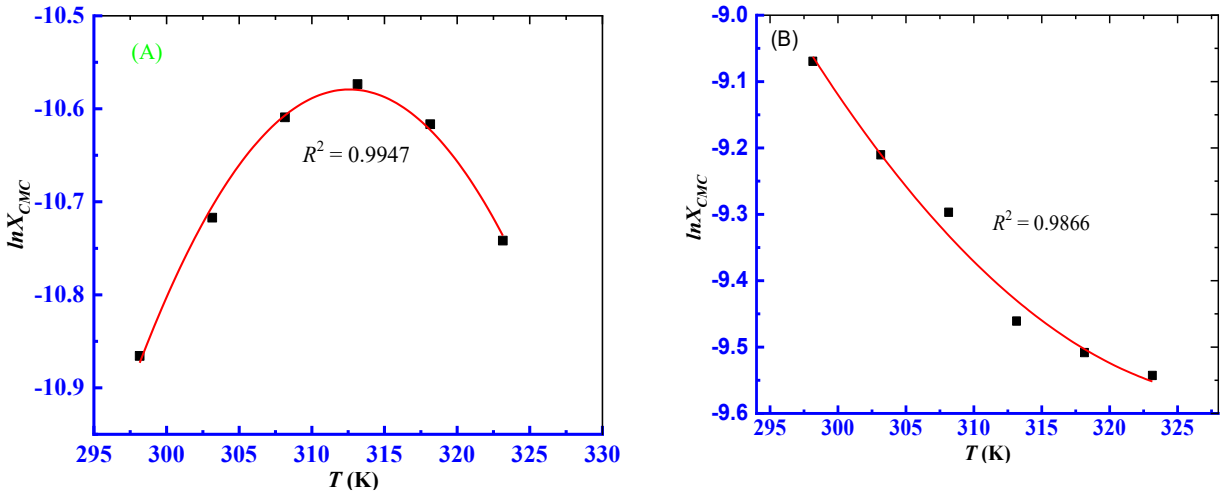


Fig. 21. Plot of lnX_{CMC} versus T for CPC + CTS in (A) aqueous and (B) aq. NaBenz media.

Table 4. The fitting variables (A, B and C) acquired from lnX_{CMC} versus T plot in water and aq. Na-salts medium

Medium	c_{salt}	A	B	C	R^2
	mmol kg^{-1}		K^{-1}	K^{-2}	
H_2O	0.00	-148.31	0.8812	-0.0014	0.9947
NaCl + H_2O	5.01	-195.85	1.1732	-0.0019	0.9892
Na_2SO_4 + H_2O	1.67	156.43	-1.1009	0.0018	0.9324
NaBenz + H_2O	5.01	44.135	-0.325	0.0005	0.9866

NaBenz HDT which reveal the less spontaneity of micellization and this result is consistent with the delayed micellization (greater *CMC* value). The $-\Delta G_m^o$ values for the micellization of CPC + CTS mixture follow the trend: $-\Delta G_m^o$ (aq.Na_2SO_4) > $-\Delta G_m^o$ (aq. NaCl) > $-\Delta G_m^o$ (aq. medium) > $-\Delta G_m^o$ (aq. NaBenz).

The values of ΔH_m^o and ΔS_m^o were negative and positive at lower and higher working temperatures for both aqueous and NaCl medium (Table 5). The opposite trend was detected in aq. Na_2SO_4 and aq. NaBenz media. The significance of ΔH_m^o and ΔS_m^o is that the enthalpy contributes only to the micellization at lower temperature while the micellization process becomes entropy controlled at higher investigated temperatures; the results observed in case of aqueous and NaCl medium. However, the opposite trend has perceived in the circumstance of aq. Na_2SO_4 solution. Noticeably, for NaBenz medium, the values of ΔH_m^o and ΔS_m^o are positive while

Table 5. Thermodynamics variables for the micellization of CPC + CTS mixture in water and aq salts/HDT media.

Medium	c_{salt}	T	ΔG_m^0	ΔH_m^0	ΔS_m^0
	mmol kg^{-1}	K	kJ mol^{-1}	kJ mol^{-1}	J mol^{-1} K^{-1}
H_2O	0.00	298.15	-43.90	-55.87	-40.15
		303.15	-42.68	-39.09	11.84
		308.15	-42.95	-22.93	64.96
		313.15	-42.67	-5.535	118.6
		318.15	-43.53	12.55	176.3
		323.15	-41.27	29.32	218.5
NaCl + H_2O	5.01	298.15	-48.32	-48.17	0.5147
		303.15	-46.36	-25.30	69.46
		308.15	-46.00	-2.711	140.5
		313.15	-44.17	20.10	205.2
		318.15	-45.02	44.25	280.6
		323.15	-46.30	69.90	359.6
Na_2SO_4 + H_2O	1.67	298.15	-56.64	37.68	316.4
		303.15	-56.14	12.93	227.8
		308.15	-59.08	-12.26	151.9
		313.15	-57.64	-38.37	61.54
		318.15	-59.40	-68.44	-28.41
		323.15	-53.94	-89.99	-111.5
NaBenz + H_2O	5.01	298.15	-31.02	27.38	195.9
		303.15	-32.50	23.37	184.3
		308.15	-33.35	18.62	168.6
		313.15	-34.73	13.62	154.4
		318.15	-34.71	7.955	134.1
		323.15	-34.61	2.168	113.8

the values decreased with rise of temperature. Consequently, the dominating factor in this case is guessed to be only entropy. The negative and positive values of ΔH_m^o represents the formation and destruction of supramolecular interactions (ion-ion, ion-dipole, dipole-dipole etc.), while only positive result indicates the occurrence of hydrophobic interaction in amongst the participated molecules [34]. However, when

both negative ΔH_m^o and positive ΔS_m^o are appeared in the result, it is considered for hydrophobic interactions in addition to electrosatic interactions [35]. The existence of both hydrophobic and electrostatic interactions was recommended previously for the study of TTAB/ CTAB with diclofenac sodium [36], where ΔH_m^o and ΔS_m^o showed negative sign in presence of ethanol.

3.1.6.2. Thermodynamic parameters of CPC + CTS mixture in aq. Nonionic hydrotropes media

For the association of CPC + CTS mixture in aq. nonionic hydrotropes media, the A, B and C regression constants are provided in (Table 6) and the lnX_{CMC} versus T plots are given in Figure 22. The values of $\Delta G_{m,}^o$ ΔH_m^o and ΔS_m^o for CPC + CTS mixture are given in **Table 7.** The negative ΔG_m^o values were obtined in all the media studied which indicates that the micellization in the study media were spontaneous. In these solvents media, the negative ΔG_m^o demonstrate the order:

$-\Delta G_m^o$ (aq. Glycerol) > $-\Delta G_m^o$ (aq. Glucose) > $-\Delta G_m^o$ (aq. Resorsinol) > $-\Delta G_m^o$ (aq. Maltose)> $-\Delta G_m^o$ (aq. ChCl) > $-\Delta G_m^o$ (aq. Urea) > $-\Delta G_m^o$ (aq. Galactose) > $-\Delta G_m^o$ (aq. 4-ABA) > $-\Delta G_m^o$ (aq. Caffeine).

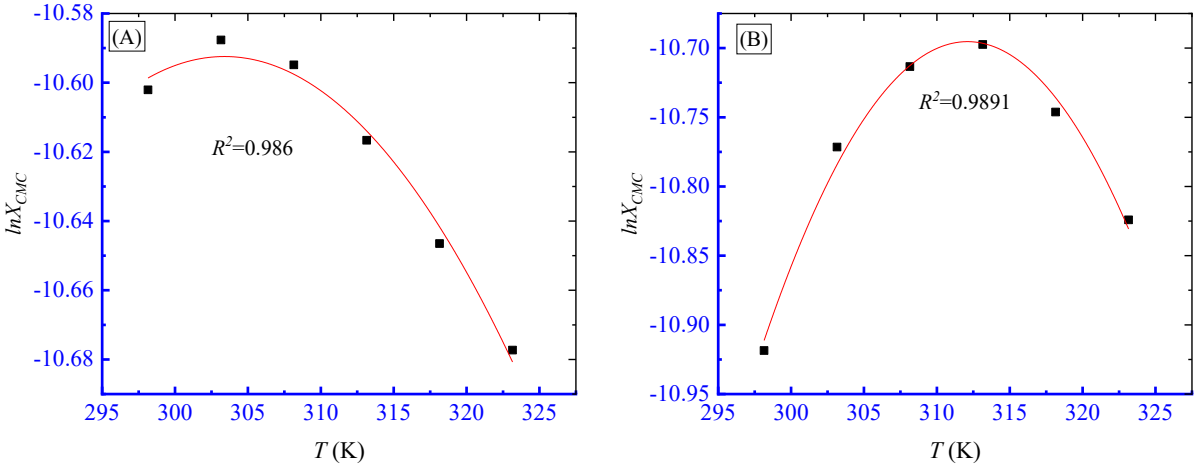


Fig. 22. Plot of lnX_{CMC} versus T for CPC + CTS in (A) aq.Caffeine and (B) aq. Glucose media.

Table 6. The fitting variables (A, B and C) acquired from lnX_{CMC} versus T plot in and aq. NIH medium at study temperature range from 298.15 to 223.15 K.

Medium	c_{salt}	A	B	C	R^2
	mmol kg^{-1}		K^{-1}	K^{-2}	
Urea + water	399.072419	-27.905	0.1241	-0.0002	0.9654
Glycerol + water	5.4992224	-60.751	0.3431	-0.0006	0.9792
4-ABA + water	4.9828951	52.665	-0.4131	0.0007	0.9797
Glucose + water	248.52924	-118.72	0.6923	-0.0011	0.9891
Galactose + water	25.0247971	-1.1759	-0.0801	0.0002	0.9753
Maltose + water	20.0000022	-107.86	0.6298	-0.0001	0.9973
CholinCl + water	29.6083541	8.8807	-0.1572	0.0003	0.97
Resorsinol + water	20.0995072	-32.805	0.148	-0.0003	0.9868
Caffeine + water	4.98394385	-31.404	0.1372	-0.0002	0.986

The values of ΔH_m^o and ΔS_m^o are positive in aq. resorcinol and glycerol solutions within the whole range of inspected temperatures. Thus, the micellization of CPC + CTS mixture in these two solvents is endothermic in nature and happened from the entropy contribution only. In aq. galactose and maltose solutions, the values of ΔH_m^o and ΔS_m^o are at all temperatures inspected. Thus, the micellization of CPC + CTS mixture in these two solvents is exothermic in nature and happened from the enthalpy contribution only. In the circumstances of aq. caffeine, 4-ABA and cholineCl solutions, ΔH_m^o and ΔS_m^o are negative and positive respectively at all temperatures studied which reveal that the micellization of employed system is exothermic in behaviour and the process is happened form the combined contribution from enthalpy and entropy. In aq. glucose and urea solutions, the ΔH_m^o and ΔS_m^o values are negative and positive at lower and higher working temperatures respectively. The significance of ΔH_m^o and ΔS_m^o indicates that the enthalpy contributes only to the micellization at lower temperature while at higher temperatures the micellization process becomes entropy controlled in case of aq. urea and glucose medium.

Table 7. The values of Thermodynamic parameters of CPC + CTS mixture in aq. nonionic hydrotropes media.

Medium	c_{salt}	T	ΔG_m^0	ΔH_m^0	ΔS_m^0
	mmol kg^{-1}	K	kJ mol^{-1}	kJ mol^{-1}	J mol^{-1} K^{-1}
Urea + water	399.1	298.15	-37.91	-5.187	109.7
		303.15	-40.59	-3.320	122.9
		308.15	-42.52	-1.035	134.6
		313.15	-40.95	1.390	135.2
		318.15	-41.58	3.883	142.9
		323.15	-42.25	6.496	150.8
Glycerol + water	5.499	298.15	-42.04	17.14	198.5
		303.15	-41.84	24.49	218.8
		308.15	-45.58	34.54	260.0
		313.15	-47.91	44.76	295.9
		318.15	-49.72	55.01	329.2
		323.15	-51.03	65.56	360.8
4-ABA + water	4.983	298.15	-37.08	-4.555	109.1
		303.15	-39.00	-12.70	86.73
		308.15	-39.30	-21.10	59.03
		313.15	-39.51	-29.92	30.63
		318.15	-39.36	-38.88	1.497
		323.15	-38.80	-47.78	-27.80
Glucose + water	248.5	298.15	-39.79	-39.51	0.915
		303.15	-44.52	-31.79	42.00
		308.15	-45.84	-18.95	87.27
		313.15	-45.95	-4.533	132.3
		318.15	-46.62	10.53	179.6
		323.15	-47.40	26.36	228.3

Table 7 (Continued).

Medium	c_{salt}	T	ΔG_m^0	ΔH_m^0	ΔS_m^0
	mmol kg^{-1}	K	kJ mol^{-1}	kJ mol^{-1}	J mol^{-1} K^{-1}

Galactose + water	25.02	298.15	-42.84	-45.44	-8.720
		303.15	-44.26	-50.32	-19.98
		308.15	-44.94	-54.86	-32.19
		313.15	-45.69	-60.01	-45.73
		318.15	-45.06	-63.50	-57.96
		323.15	-45.57	-68.29	-70.29
Maltose + water	20	298.15	-43.44	-678.4	-2130
		303.15	-43.05	-687.1	-2125
		308.15	-43.90	-713.2	-2172
		313.15	-45.04	-739.9	-2219
		318.15	-46.60	-771.9	-2280
		323.15	-50.87	-844.0	-2454
ChCl + water	29.61	298.15	-43.73	-25.01	62.81
		303.15	-44.81	-29.62	50.12
		308.15	-41.43	-31.92	30.86
		313.15	-42.42	-37.28	16.40
		318.15	-42.00	-41.68	1.020
		323.15	-42.88	-47.78	-15.18
Resorsinol + water	20.10	298.15	-48.80	40.18	298.4
		303.15	-48.61	44.54	307.2
		308.15	-48.09	48.64	313.9
		313.15	-47.41	52.36	318.6
		318.15	-46.49	55.95	322.0
		323.15	-45.78	59.36	325.4
Caffeine + water	4.984	298.15	-38.11	-19.23	63.33
		303.15	-39.49	-18.02	70.82
		308.15	-39.36	-15.96	75.94
		313.15	-39.53	-13.92	81.77
		318.15	-39.71	-11.79	87.73
		323.15	-39.30	-9.444	92.39

It has been proposed by Nusselder and Engberts [37] that the London-dispersion forces are responsible for the micellar process to happen owing to the negative enthalpy values**.** In the single surfactant system positive and negative values of enthalpy were also earlier obtained by Rub et al. [38-40]. There are two reasons that might be

considered to explain the positive values of ΔS^0_m for surfactant micellization mediated by CTS. First, the iceberg formations are destroyed as hydrophobic chains are transferred from their hydrated state in an aqueous medium to the nonpolar core of the micelle. Secondly, the rotational degree of freedom of the hydrophobic chains in the micelle interior is intensified in comparison to the aquatic environment [41-42]. When iceberg structure formation surrounding the CTS and CPC is more prominent than the other two effects combined, negative values of ΔS^0_m may be observed. A negative ΔH^0_m could happen when the hydrophilic head group's hydration becomes more significant than the hydrophobic alkyl chains of surfactant monomers' water structure [43-44]. Thus, the recommended interaction forces among study components are hydrophobic and ion- induced dipole interactions in the used media.

3.1.7. Thermodynamics of transfer

3.1.7.1. Thermodynamic transfer of CPC + CTS mixture in aq. Na-salts media

The thermodynamics of transfer variables in aqueous NaCl and Na_2SO_4 media are given in Table 8. The $-\Delta G^o_{m,t}$ values indicate that the micellization processes in presence of these two simple electrolytes were more spontaneous than the occurring of the process in water. On the other hand, the $\Delta G^o_{m,t}$ was positive in NaBenz medium throughout the temperature studied which imply that the aggregation experience low spontaneity in NaBenz medium. The values of $\Delta H^o_{m,t}$ and $\Delta S^o_{m,t}$ were positive for NaCl medium that indicating an endothermic process, and the absorbed energy from the surrounding may use for the water structure destruction that ultimately disrupts the hydrophobic interaction. However, in aq. Na_2SO_4 and aq. NaBenz media, the values of $\Delta H^o_{m,t}$ and $\Delta S^o_{m,t}$ were positive at lower temperatures and negative at higher temperatures. Thus the results demonstrate the transition of an endothermic process to exothermic with the rise of temperature.

Table 8. Values of the thermodynamics of transfer for the micellization of CPC + CTS mixture.

Medium	c_{salt}	T	$\Delta G^0_{m,t}$	$\Delta H^0_{m,t}$	$\Delta S^0_{m,t}$

	mmol kg^{-1}	K	kJ mol^{-1}	kJ mol^{-1}	J mol^{-1} K^{-1}
NaCl + H_2O	5.01	298.15	-4.417	7.706	40.66
		303.15	-3.685	13.78	57.63
		308.15	-3.051	20.22	75.50
		313.15	-1.498	25.63	86.64
		318.15	-1.492	31.70	104.3
		323.15	-5.028	40.58	141.1
Na_2SO_4 + H_2O	1.67	298.15	-12.74	93.55	356.5
		303.15	-13.46	52.02	216.0
		308.15	-16.14	10.67	86.98
		313.15	-14.97	-32.84	-57.04
		318.15	-15.87	-80.99	-204.7
		323.15	-12.67	-119.3	-330.0
NaBenz + H_2O	5.01	298.15	12.88	83.26	236.1
		303.15	10.18	62.46	172.5
		308.15	9.599	41.55	103.7
		313.15	7.938	19.16	35.83
		318.15	8.819	-4.593	-42.16
		323.15	6.657	-27.16	-104.6

3.1.7.2. Thermodynamic transfer of CPC + CTS mixture in aq. Nonionic hydrotropes media

The thermodynamics of transfer variables in aq. Nonionic hydrotropes media are given in Table 9. The $\Delta G^{o}_{m,t}$ values have been detected as negative in aqueous 4-ABA, cholineCl and caffeine media, which indicates that the micellization process in presence

Table 9. Values of the thermodynamics of transfer for the micellization of CPC + CTS mixture in aq. Nonionic hydrotropes media

Medium	c_{salt}	T	$\Delta G^{0}_{m,t}$	$\Delta H^{0}_{m,t}$	$\Delta S^{0}_{m,t}$
	mmol kg^{-1}	K	kJ mol^{-1}	kJ mol^{-1}	J mol^{-1} K^{-1}
Urea + water	399.1	298.15	-5.995	-50.68	-149.9
		303.15	-2.091	-35.77	-111.1
		308.15	-0.4314	-21.90	-69.66
		313.15	-1.719	-6.925	-16.61
		318.15	-1.955	8.667	33.42
		323.15	0.9787	22.82	67.66
Glycerol + water	5.499	298.15	-1.862	-73.01	-238.6
		303.15	-0.8440	-63.58	-207.0
		308.15	2.626	-57.47	-195.0
		313.15	5.245	-50.30	-177.3
		318.15	6.190	-42.46	-152.9
		323.15	9.760	-36.24	-142.3
4-ABA + water	4.983	298.15	-6.821	-51.31	-149.2
		303.15	-3.684	-26.39	-74.89
		308.15	-3.655	-1.825	5.928
		313.15	-3.157	24.39	87.97
		318.15	-4.172	51.43	174.8
		323.15	-2.474	77.10	246.3
Glucose + water	248.5	298.15	-4.114	-16.36	-41.06
		303.15	1.843	-7.300	-30.16
		308.15	2.887	-3.984	-22.31
		313.15	3.284	-1.002	-13.67
		318.15	3.087	2.020	-3.323
		323.15	6.132	2.956	-9.773

Table 9.(Continued)

Medium	c_{salt}	T	$\Delta G^{0}_{m,t}$	$\Delta H^{0}_{m,t}$	$\Delta S^{0}_{m,t}$

	mmol kg^{-1}	K	kJ mol^{-1}	kJ mol^{-1}	J mol^{-1} K^{-1}
Galactose + water	25.02	298.15	-1.062	-10.43	-31.43
		303.15	1.580	11.23	31.82
		308.15	1.987	31.93	97.15
		313.15	3.023	54.48	164.3
		318.15	1.528	76.05	234.3
		323.15	4.305	97.61	288.8
Maltose + water	20.00	298.15	-0.4583	622.6	2090
		303.15	0.3720	648.0	2136
		308.15	0.9462	690.3	2237
		313.15	2.365	734.3	2337
		318.15	3.073	784.4	2456
		323.15	9.598	873.3	2673
CholinCl + water	29.61	298.15	-0.1655	-30.86	-103.0
		303.15	2.132	-9.473	-38.28
		308.15	-1.525	8.986	34.10
		313.15	-0.2535	31.75	102.2
		318.15	-1.529	54.23	175.3
		323.15	1.605	77.10	233.7
Resorsinol + water	20.10	298.15	4.900	-96.05	-338.6
		303.15	5.925	-83.63	-295.4
		308.15	5.136	-71.57	-248.9
		313.15	4.738	-57.90	-200.0
		318.15	2.963	-43.40	-145.7
		323.15	4.507	-30.04	-106.9
Caffeine + water	4.984	298.15	-5.793	-36.64	-103.5
		303.15	-3.186	-21.07	-58.98
		308.15	-3.592	-6.972	-10.98
		313.15	-3.144	8.386	36.83
		318.15	-3.823	24.34	88.57

of these non-ionic hydrotropes become more spontaneous in comparison to water medium. The $\Delta G^{o}_{m,t}$ values were acquired to be positive, in aqueous resorcinol, glycerol, glucose, galactose, maltose, glycerol and urea media, which indicates that the

micellization process in presence of these non-ionic hydrotropes was less spontaneous than the happening of the process in water medium. Additionally, it was discovered that the transfer of resorcinol and glycerol from water to an aqueous urea solution had negative transfer enthalpies [45-46]. Both negative and positive values of $\Delta H^0_{m,t}$ and $\Delta S^0_{m,t}$ are obtained in the aq. solution of nonionic hydrotropes media where $-\Delta H^0_{m,t}$ and $+\Delta H^0_{m,t}$ values dictate the more exothermic and endothermic nature of the micellization process [47-48].

3.1.8. Enthalpy-entropy compensation of CPC and CTS drug mixture in aqueous and aq. Additives media

In the case of micellization of amphiphilic substances, the enthalpy-entropy compensation has beeb characterized from the linear plots of enthalpy vs entropy of micellization (Figure 23). The compensation variables such as $\Delta H_m^{o,*}$ and T_c values are listed in Tables 10a and 10b. The negative values $\Delta H_m^{o,*}$ for all the mediums studied indicate a more stable state after the formation of micelle. Here, the more negative values appeared for Na_2SO_4 (-57.60 kJ mol^{-1}), while minimum values were exhibited by NaBenz (-33.16 kJ mol^{-1}). This result suggested that in terms of stability of CPC + CTS mixture should be more stable in presence of Na_2SO_4 while for aq. NaBenz medium this stability was the lowest. Similar maximum stability for Na_2SO_4 medium was previously reported for the micellization of surfactant system [5]. The estimated T_c values for CPC + CTS mixture were maximum (329.51 K) for NaCl containing medium, while for aqueous, aq. Na_2SO_4, and aq. NaBenz media; the T_c values were 324.84, 302.97, and 307.09 K, respectively. Usually, the T_c values within the range of 311.2-312.8 K represent the existence of zwitter ion [49]. As the values of T_c, for the aq. protein and small solutes solutions, lie in between 270 to 330 K temperatures, therefore this surfactant system can be used for the estimation of H_2O content in the biological system [50]. The reported the T_c values of 332, 283, and 343 K in H_2O, aq. sodium salicylate, and aq. NaCl solutions, respectively for cationic gemini surfactant

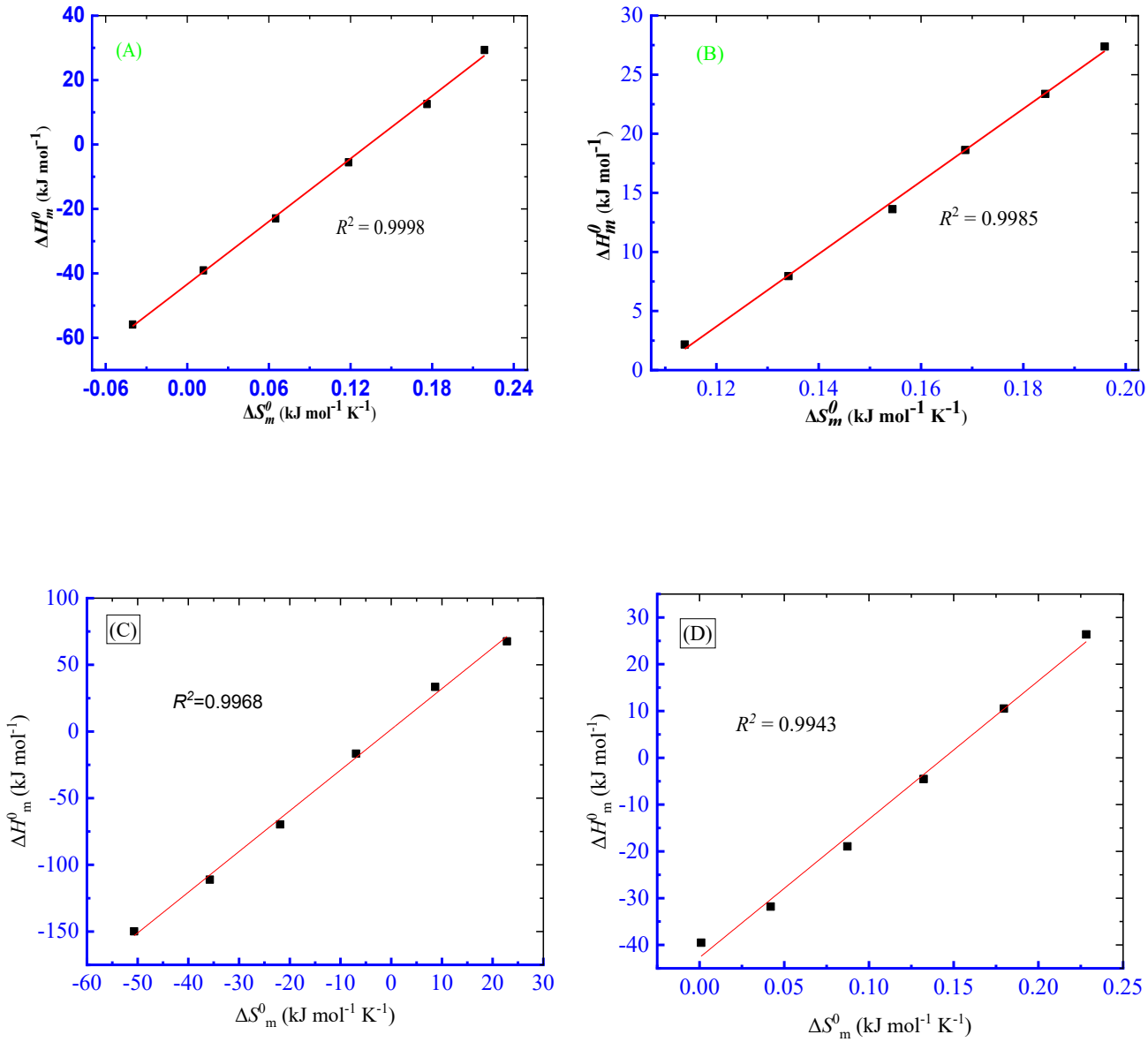


Fig. 23. The ΔH_m^0-ΔS_m^0 plot for the assembly of CPC + CTS mixture in (A) water, (B) aq. NaBenz, (C) aq. Urea, and (D) aq. Glucose media.

Table 10a. The variables for the ΔH_m^0-ΔS_m^0compensation associated with the micellization of CPC + CTS mixture.

Medium	c_{salt}	$\Delta H_m^{0,*}$	T_c	R^2
	mmol kg^{-1}	kJ mol^{-1}	K	

H_2O	0.00	-43.37	324.84	0.9998
NaCl + H_2O	5.01	-48.307	329.51	0.9999
Na_2SO_4 + H_2O	1.67	-57.60	302.97	0.9991
NaBenz + H_2O	5.01	-33.16	307.09	0.9985

Table 10b. The variables for the ΔH_m^0-ΔS_m^0 compensation associated with the micellization of CPC + CTS mixture in nonionic hydrotropes solutions.

Medium	c_{salt}	$\Delta H_m^{0,*}$	T_c	R^2
	mmol kg^{-1}	kJ mol^{-1}	K	
Urea + water	399.1	-38.292	291.34	0.9286
Glycerol + water	5.499	-40.432	291.07	0.9976
4-ABA + water	4.983	-39.345	313.01	0.9994
Glucose + water	248.5	-42.694	295.78	0.9943
Galactose + water	25.02	-42.784	364.91	0.9974
CholinCl + water	29.61	-42.376	280.58	0.9807
Caffeine + water	4.984	-41.623	341.9	0.979

[51]. Moghaddam and co-workers [52], obtained enthalpy-entropy compensation for the micellization of different non-ionic surfactants and the reported T_c values for the respective surfactants in aq. medium were in the range 309.5− 314.4 K. The T_c values have been taken as a proof of the existence of hydrophobic interaction amid solute and solvent for a specific system [53-54].

3.2. Exploration of the Clouding phenomena

3.2.1. Assessment of Cloudy development of TX-100 and CTS drug mixture in an aq. Medium

The occurrence of clouding and its characteristic behavior in a drugs-surfactant system depends on the spherical size of micelles, aggregation number, and charge of the micelles. Figure 24 shows the rising of CP with the addition of CTS drug at fixed concentration of triton X-100 solution. In the designated mixtures, the surfactant might be appeared either in monomer form or in an associated form. The surfactant monomers are surrounded by drug monomers in solutions which can inhibit the growth of micelles. The CTS drug added into the TX-100 surfactant solution forms drug-surfactant mixed micelle. Since the triton X-100 is a non-ionic surfactant with the oxyethylene unit in its structures, which is hydrophilic in nature, the interactions between the CTS drug and surfactant predominantly proceed through the hydration process leading to the development of micelles species. This strong hydration interaction could be disrupted only at higher temperatures which caused the dehydration of the mixed micelles. As a result, the clouding occurred in the corresponding surfactant-drug solutions at relatively elevated temperatures.

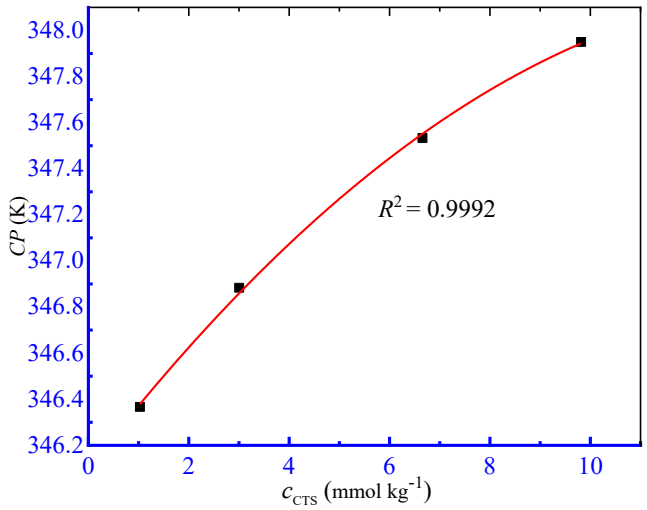


Fig. 24. The plot of CP versus concentrations of CTS drug in aqueous medium.

An increase in concentrations of CTS drug while keeping the constant extent of surfactant triton X-100 in the resulting mixtures causes a rise in CP of the TX-100 + CTS mixtures. The result showed the increase of solubility of TX-100 in water with increasing CTS drug concentration. Hydrophobicity character of TX-100 surfactant monomers also played an important rule to develop the clouding phenomena in the triton X-100 and CTS mixtures. Above *CMC*, there might have potential co-existence

of both drug micelles and surfactant micelles in the resulting solutions which experienced a relatively higher inter-micellar repulsion that resulted the subsequent enhancement of the magnitudes of CP in the respective solutions.

3.2.2. Effect of Na-salts on the CP values of TX-100 and CTS drug mixture

The determination of CP in surfactant solutions in the presence of other chemical entities such as drugs, additives is sometimes crucial because of the existence of various interactions among different chemical species in the respective mixtures as well as the unequal distribution of chemical entities with the separation of two isolated phases at above CP temperature. The investigation of cloud point behaviors of TX-100 + CTS drug systems at different concentrations of sodium salt electrolytes and hydrotropic salts solutions provided interesting and quite impressive results. The CP values

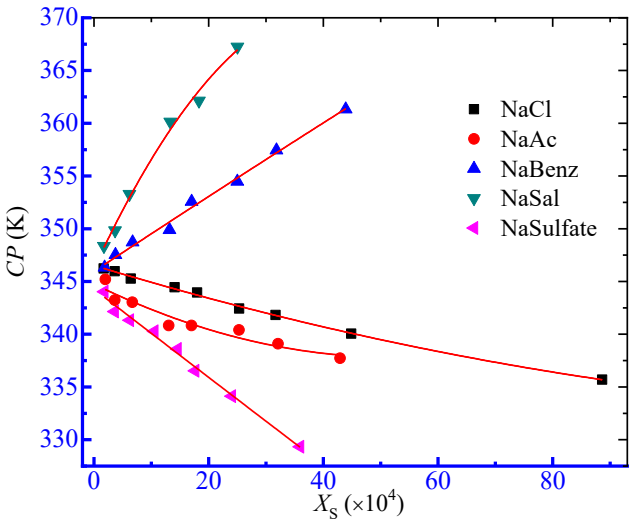


Fig. 25. The plot of CP versus X_{salt} (×10^4) for the aqueous mixture of CTS and TX-100 in the presence of various electrolytes and hydrotropic salts solutions.

measured in the TX-100 + CTS drug mixtures in attendance of inorganic salts and hydrotropic salts have been displayed in the Figure 25. The attendance of inorganic salts or hydrotropic salts into TX-100 + CTS drug mixtures may either increase CP or decrease the CP value. The particular concentrations of TX-100 (80 mmol kg^{-1}) and CTS drug (3 mmol kg^{-1}) were used to investigate the nature and characteristics of clouding in the corresponding mixtures and there were no changes in the concentrations

of both surfactant and drug during all experiment studies. The clouding behaviors of TX-100 + CTS system were found to be highly varied due to the interferences of different aqueous inorganic salts media such as NaCl (ionic strength identical to 9.378-497.0), NaOAc (ionic strength identical to 11.09-239.6), Na_2SO_4 (ionic strength identical to 30.11-601.2), hydrotropic salts like NaBenz (ionic strength identical to 10.32-245.0), and NaSal (ionic strength identical to 10.32-139.3). The ionic charge has played a significant role to change the degree of CP in the resulting mixtures. The extents of CP were found to be decreased with the increase in concentrations of inorganic salts solutions such as NaCl, NaOAc, and Na_2SO_4 respectively. Similar studies conducted previously on other surfactant-drug systems in salts solutions also displayed the decreasing trend of CP with the rise of electrolytes concentrations [55-58]. It has been noticed that on the addition of Na_2SO_4 electrolyte, the expected CP values have been decreased more than those observed with NaCl solutions. This might be due to the actions of NaCl as a lesser effective depressor in comparison to the activity of Na_2SO_4 [59]. Previous studies from Parikh *et al.* [60] reported the lowering of CP values in TX-100 and TX-114 system on the cumulative addition of NaCl and Na_2SO_4 solutions. The extents of CP were also observed to be decreased for the Tween-80 solutions in attendance of NaCl as reported from the previous studies conducted by Joshi and Dave [61]. Similarly, the decreasing trend in the degree of CP was realized with TX-100 solutions in the presence of NaCl solution [62]. Ahmed *et al.* [63] observed very sharp decrease in the magnitudes of CP for the phase separation of the mixture of X 100 and sodium alginate biopolymer mixture due to the addition of sodium based inorganic salts (NaCl, Na_2SO_4 and Na_3PO_4). In that investigation, NaCl was found as the most effective CP suppressor among the three Na-based electrolytes employed. The findings of CP from the present investigation on the TX-100 + CTS systems with different sodium salts were highly comparable to the data reported previously in the literatures [60-62]. The CP value of TX-100 + CTS mixtures were found to be highly varied with the concentrations of different electrolytes and followed the order of: $CP_{aq.\ NaCl} < CP_{aq.\ NaOAc} < CP_{aq.\ Na_2SO_4}$. Inorganic salts like sodium chloride, sodium sulfate constitute and maintain the electrolytic balance in biological fluids in various cells of human bodies. The phase separation behaviors of surfactants solutions are highly significant to utilize them as potential drug carriers. The appropriate mechanism in favor of decreasing the CP contents is assumed to be related

to the strengths of anions and their relative position in the Hofmeister series [64]. Anions work as the most effective depressors in reducing the CP of surfactant-drug mixtures in comparison to the functions of cations, because they form relatively strong interaction with solvents and form water structures in the respective solutions.

The electrolytes which induce the salting-out effect in surfactants solutions may reduce the cloud point and on the other hand salting-in electrolytes exhibit the opposite effect on cloud points assessment. The sulfate ion in the sodium electrolyte solutions used in the present study is located at the left side in the Hofmeister series and thus work as water structure makers in the studied surfactant-drug system. The sulfate ion could facilitate the aggregation of water molecules and thus reduced the solubility of the TX-100 surfactant in water which might have resulted in the reduction of the CP values. On the contrary, chloride ion is being placed at the right side in the Hofmeister series which function as water structure breaker ion by splitting the 3D water structure and thus increase the solvation power of water molecules. The chloride ions have potential ability to inhibit the growth of self-aggregation of water molecules which causes the acceleration of the H-bond formation between water molecules and hydrophilic part of the non-ionic surfactant. This salting-in effect caused by chloride ions might have resulted in the subsequent rise in the CP values of the TX-100 + CTS system. Furthermore, the enhancement in CP was realized on the addition of anionic hydrotropic salts such as sodium salicylate and sodium benzoate into TX-100 + CTS drug mixtures. The anionic hydrotropes possess ion with negative charge (- COO^-), which is directly attached to the benzene ring. On the other hand, the structure of ceftriaxone sodium drug is endowed with positive charge. The interactions between hydrotrope and drug was assumed to be electrostatic as well as hydrophobic both of which might have contributed to decrease the CP in the resulting mixtures. However, a dramatic increase in the degree of CP was realized when sodium salicylate and sodium benzoate were applied to the surfactant-drug systems under different experimental conditions. Similar variation in the magnitudes of CP were also observed in other studies conducted previously by several research groups [65-67]. Rub *et al.* [68] reported the sharp increase in the magnitudes of CP within the triton X-100 (TX-100) and metformin hydrochloride (MNH) drug mixture due to the influence of cumulative rise in concentration of anionic hydrotropes (NaSal and NaBenz). The findings of CP from the present investigation were quite interesting and more or less similar to the data

reported previously in literatures from other surfactant-drug systems [65-68]. The persistence of electrostatic interactions between head groups of hydrotropic and CTS drug might have hindered the aggregation of micelles which caused the corresponding increase in CP in the respective mixtures. The monomers of hydrotropes can be adsorbed on the surface of associated drug mediated micelles which may potentially interfere drug species to aggregate [67]. The magnitudes of CP in the studied surfactant-drug mixtures are highly dependent on the natures and structures of hydrotropes. The structural moieties of sodium salicylate are endowed with $COO-$ and $-OH$ functional groups which turned the compound to be more hydrophilic. This might have caused the appearance of relatively lower extents of CP in the TX-100 + CTS mixture in sodium salicylate in comparison to those observed with sodium benzoate solution (Figure 25) [69]. The results of the present study revealed that both inorganic salts and hydrotropic salts created strong impact on the development of CP in the TX-100 + CTS drug systems (Figure 25) and caused the declining of the corresponding CP values with increasing in their respective concentrations and the variations of CP in the attendance of various additives were found to be in the order of: $CP_{aq.\ NaSal} < CP_{aq.\ NaBenz} < CP_{aq.\ NaCl} < CP_{aq.\ NaOAC} < CP_{aq.\ Na_2SO_4}$.

3.2.3. Effect of K-salts on the CP values of TX-100 and CTS drug mixture

The nonionic surfactants (NISs) species demonstrate the characteristic behavior in solution phase. These species exhibit the development of cloudy by separating the NIS solution into two phases ((a) surfactant rich phase and (b) surfactant less phase) at a certain temperature (CP) at a definite experimental environment. TX-100 molecules have the ability to create micelle at about 0.2 to 0.3 mmol kg^{-1} in H_2O environment [70]. Nevertheless, in this exploration, the higher contents of TX-100 (80 mmol kg^{-1}) have been considered so that entirely TX-100 molecules would have the opportunity to happen in the aggregated form. Drugs or mixtures of drug components might have an impact on the CP values of NISs also at very low concentrations [71-72]. To investigate the CP of TX-100 (80 mmol kg^{-1}) and CTS mixture, the concentration of CTS drug was kept fixed and equal to (3.1 mmol kg^{-1}). The consequences of the several potassium salts (e.g. KCl, K_3PO_4, $KBrO_3$, K_2SO_4, and KI) on the CP values of the working system

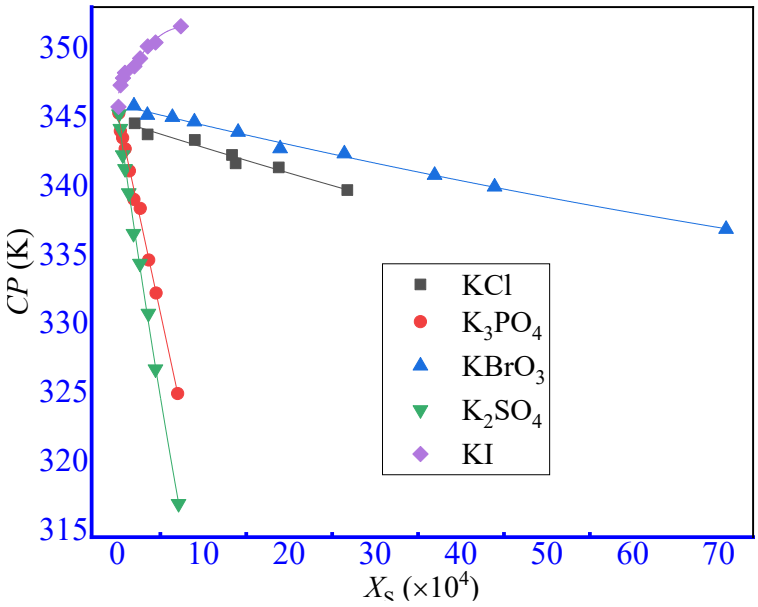
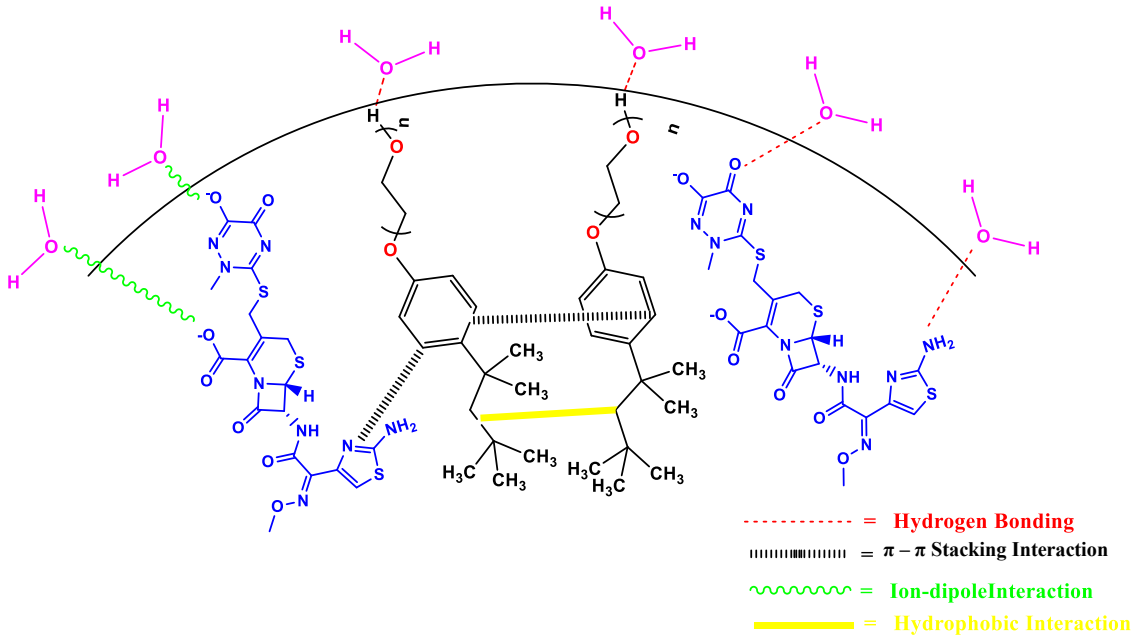


Fig. 26. The plot CP versus X_{salt} (×10^4) for the aq. mixture of CTS and TX-100 in occurrence of salts.

have been investigated in the present research. Potassium salts are biologically important. These salts are found in the body fluid. The crucial role of these salts is to control the pH and osmotic pressure of the body fluid. That's why such inorganic salts as electrolytes were randomly selected during the experiment. In terms of ionic strength (*I*), the concentrations of KCl, K_3PO_4, $KBrO_3$, K_2SO_4, and KI range from 13.38 to 194.7, 59.95 to 2355, 10.68 to 396.6, 31.47 to 1195 and 7.125 to 413.4 mmol kg^{-1}, respectively. The CP values of TX-100 + CTS mixture in aq. inorganic salt solutions are displayed in Figure 26. The CP values of the TX-100 + CTS system were acquired to be lessened/increased with growing electrolyte contents, which may possibly be ascribed to the incidence of strong interaction between the micelles [73]. The anions may create a salt bridge in an amphiphilic solution and lose water molecules which consequences in fitting these anions between the head groups of amphiphiles [74-75]. This phenomenon causes salting out of amphiphiles from the aqueous vicinity and micelle-micelle interaction increases. The formation of anion bridge is also shown in Figure 27. According to Figure 27, the hydrogen bond between -OH of TX-100 and water molecules is eliminated by the formation of anion bridge between -OH of two

(A)


= Hydrogen Bonding
= π – π Stacking Interaction
= Ion-dipoleInteraction
= Hydrophobic Interaction

(B)

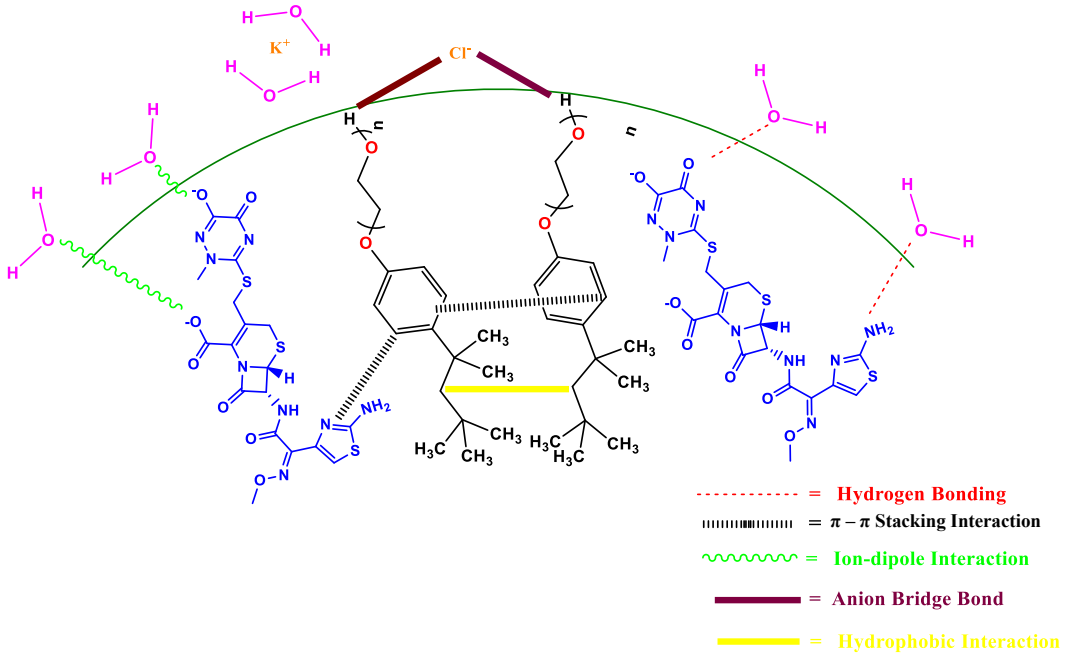


Fig. 27. The probable interactions between TX-100 and CTS drug in (A) absence of salt and (B) presence of KCl salt.

TX-100 and chloride anion. Such bridge formation might also be possible in the manifestation of the anion of K_3PO_4, $KBrO_3$, and K_2SO_4 salts. Thus, the values of the CP slowly declined in the appearance of salts as the concentrations of the respective salts exceeded for KCl, K_3PO_4, $KBrO_3$, and K_2SO_4, and vice versa for KI (Figure 26). The CP values of TX-100 + CTS mixture have been noticed to be diminished sharply in K_2SO_4 medium as compared to other salts like KCl, K_3PO_4, and $KBrO_3$. A sharp drop of CP values of TX-100 + amikacin drug in SO_4^{2-} medium as compared to Cl^- salt was also reported earlier [76]. In the earlier study, the reducing trend of CP for the clouding of TX-100 and an antidiabetic drug mixture in the appearance of potassium salts was explored [77]. A greater impact of PO_4^{3-} ion in diminishing CP values for the cloudy creation of Brij-35 (a typical NIS molecule) was described in contrast to the effect realized by divalent SO_4^{2-} and monovalent NO_3^- ions; the consequences have been detected by the examination of Batigöc and Akbas [78]. For the cloudy growth of the TX-100 and promethazine hydrochloride mixture, the lessening of CP values was also quantified in the occurrence of K-salts [79].

In the Hofmeister series, SO_4^{2-}, HPO_4^{2-}, and Cl^- anions are positioned at the left corner and these anions are considered as H_2O structure makers. Thus, the entropy of a system becomes zero due to the formation of salt anion by water molecules which results *salting-out* effect in the solution of TX-100 + CTS system (Table 13). The water molecules attaching with electrolytes salts out the NIS (amphiphiles) from the free space of the aqueous environment and the consequence is that phase separation happens earlier (there is a decrease of CP). On the contrary, Cl^- and NO_3^- anions occupy the right position of the series and it has high polarizability with low charge density. These anions show less attaching tendency with water molecules which results in *salting in* effect in the solution mixture and thus exerts growing solubility of the study mixture in the liquid systems [77]. The upsurge in CP values of TX-100 + CTS system with the augmentation of KI concentrations is caused by the "*salting in"* phenomena.

3.2.4. Effect of ammonium-salts on the CP values of TX-100 and CTS drug mixture

The impacts a variety of ammonium salts, including NH_4Cl, $(NH_4)_2SO_4.FeSO_4.6H_2O$, $(NH_4)_2SO_4$, and $(NH_4)_2HPO_4$ were examined on clouding behavior of the TX-100 + CTS system. Figure 28 illustrates the variation of the CP of the TX-100 + CTS (3 mmol kg^{-1}) mixture in aq. ammonium salts solution. The ionic strength (I) of the concentrations of NH_4Cl (AmCl), $(NH_4)_2SO_4.FeSO_4.6H_2O$ (AmFSul), $(NH_4)_2SO_4$ (AmSul) and $(NH_4)_2HPO_4$ (AmHP) were 11.25-402.1, 0.1039-7.022, 32.24-1203, and 28.91-1195 mmol kg^{-1}, respectively. The introduction of AmCl, AmSul and AmHP

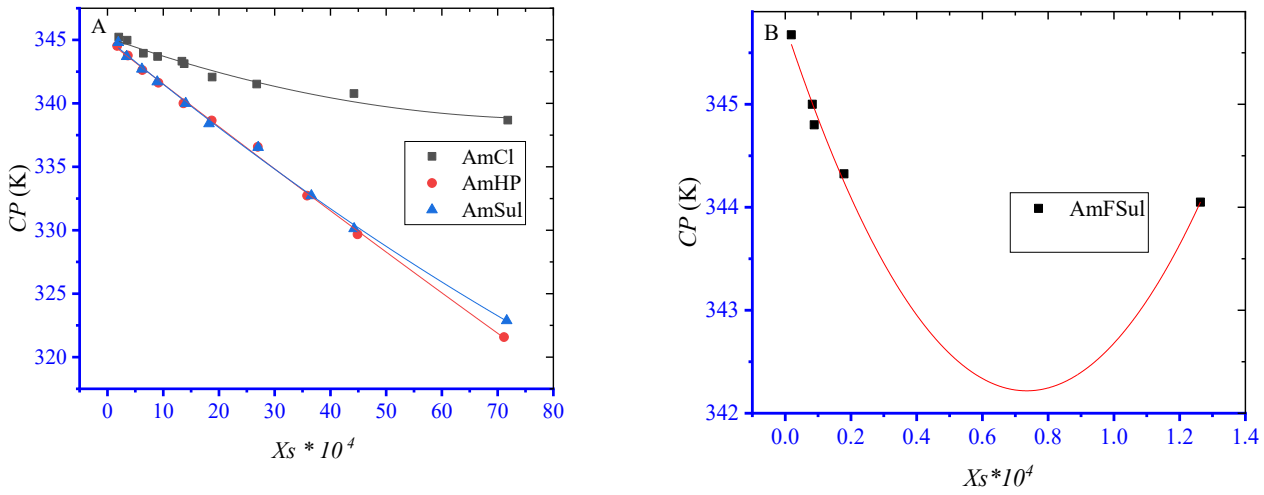


Fig. 28. The plot CP versus X_{salt} ($\times 10^4$) for the aq. mixture of CTS and TX-100 in occurrence of ammonium salts.

reduces the CP of TX-100 + CTS (3 mmol kg^{-1}) mixture with the enhancing ionic strength. In case of aq. AmFSul, the CP values reduced to a minimum value and then increased as a function of [AmFSul]. The drop of CP values for the TX-100 + CTS system with the increase of electrolyte concentration indicate the strong micelle-micelle interaction [73] Thus, in all the ammonium-based electrolytes used, the solubility of TX-100 + CTS mixture becomes lowered due to the salting out effect of the electrolytes. At highest concentration of salts used, the CP values of current system follow the trend: CP (AmCl) > CP (AmSul) > CP (AmHP). The reduction in CP values for the TX-100 + MNH combination in the presence of ammonium salts and potassium salts has been described in the earlier study [78, 83]. The anionic species SO_4^{-2}, HPO_4^{-2}, and Cl^-, which appear on the left of the anionic series in the Hofmeister series, are well known for their ability to form H_2O structures. The motion and engagement of water molecules towards the creation of salt anion leads to a salting out effect on the non-ionic surfactants TX-100 + CTS system, hence decreasing the entropies of solution systems (Table 15). Since water's dipole is drawn to electrolytes, the surfactant molecules are salt-extracted from the aqueous environment, increasing inter-micellar contact and precipitating an earlier phase separation. Gradually, CP values fall as the electrolyte level rises due to an increase in ion dipole interaction. As previously mentioned, the addition of ammonium sulphate results in a stronger inter micellar interaction and a decrease in CP values due to the greater charge density of the sulfate ion. As a result, the attractive interaction between this anion and water molecules is significantly reduced, which results in the

occurrence of the water breaking effect in solution mixtures and reduces the solubility of the surfactant in liquid systems [73].

3.2.5. Effect of nonionic hydrotropes on the CP values of TX-100 and CTS drug mixture

The impact of various nonionic hydrotropes (NIHs) on the clouding of TX-100 and CTS drug mixture has been examined. The glucose, galactose, maltose, Choline HCl, resorcinol and caffeine were used as NIHs in the present study. The acquired results of the impacts of NIHs on the clouding of TX-100 and CTS drug mixture are graphically displayed in Figures 29. The introduction of glucose, galactose, maltose, Choline HCl, and resorcinol causes the reduction of CP values while caffeine enhances the CP values of TX-100 and CTS drug mixture. Consequently, the solubility of TX-100 and CTS drug mixture in water environment experiences a reduction in the manifestation of glucose, galactose, maltose, Choline HCl, and resorcinol while caffeine augments the solubility of TX-100 and CTS drug mixture. Roy and Moulik foiund the decrease of CP value of clouding of TX-100 and methyl cellulose mixture in the appearance of resorcinol, proline and pyrogallol while the CP was augmented in presence of Sodium salicylate [80]. The augmentation of the CP values of poly(N-isopropyl acrylamide) and its hydrogel was observed due to the addition of salicylates whereas the CP values of the same system were lowered in the presence of 4-methyl catechol, resorcinol, hydroquinone, catecol and pyrogallol; the investigartion were performed by the Dhara and Chatterji [81].

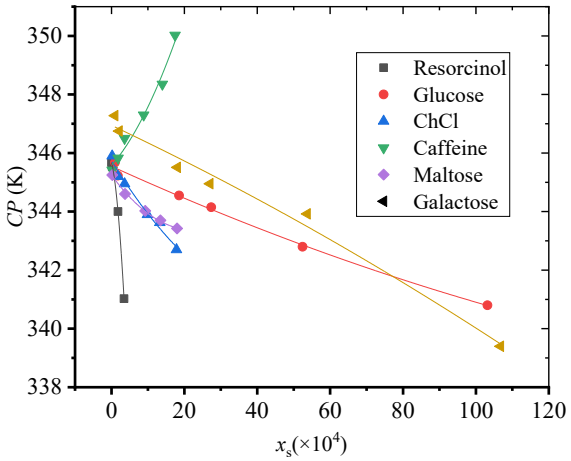


Fig. 29. The plot CP versus X_{salt} (×10^4) for the TX-100 and CTS drug mixture in occurrence of nonionic hydrotropes.

3.2.6. Thermodynamics of clouding

3.2.6.1. Thermodynamic parameters of TX-100 and CTS drug mixture aqueous and aqueous sodium salts media

The A, B, and C values determined for the TX-100 + CTS drug mixture with various electrolytes and hydrotropic salts under different experimental conditions have been presented in Tables 11 & 12. The plot of lnX_s vs. T (CP) showed the non-linear relationship for the studied surfactant-drug system (Figure 30). Table 12 summarizes the values of thermodynamic variables such as ΔG_c^0, ΔH_c^0 and ΔS_c^0 for the TX-100 + CTS drug mixtures in pure water and aq. solutions of various electrolytes / anionic hydrotropic salts. The free energy (ΔG_c^0) of clouding was obtained to be positive which indicates the nonspontaneous nature of the clouding scheme. The extents of positive ΔG_c^0 were observed to be decreased with increasing in the concentrations of electrolytes and hydrotropic salts while the concentrations of TX-100 (80.29 mmol kg^{-1}) and CTS drug (3.100 mmol kg^{-1}) were remained unchanged. The clouding process was assumed to be shifted toward the spontaneity at the expense of higher concentrations of electrolytes and hydrotropic salts solutions respectively. It was also noted that the

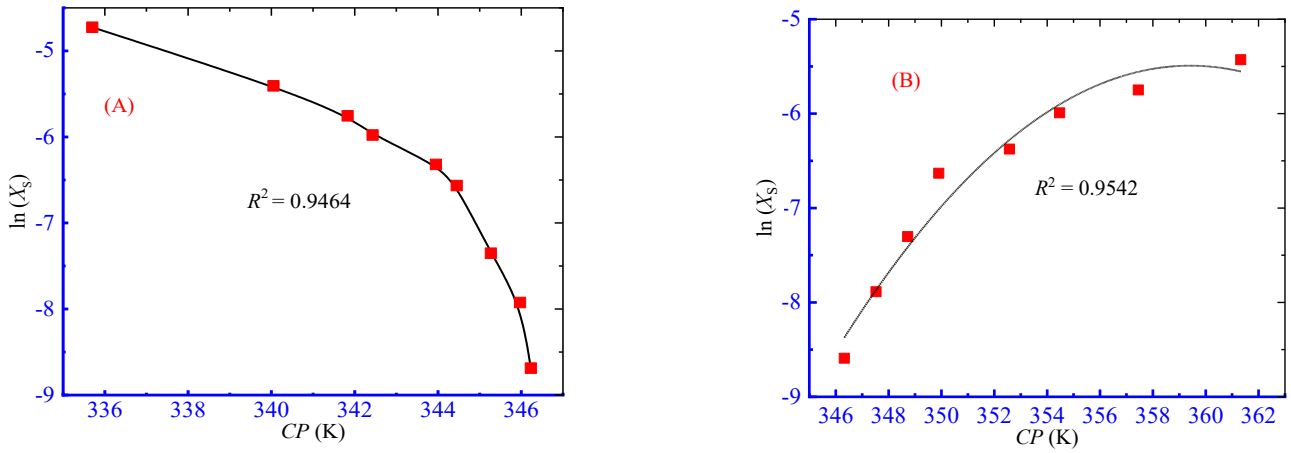


Fig. 30. lnX_s versus CP plot for the clouding of aqueous mixtures of TX-100 and CTS in: (A) H_2O + NaCl and (B) H_2O + NaBenz.

Table 11. The A, B and C values were determined from the lnX_s versus CP plot for the clouding of aqueous mixtures of TX-100 and CTS in different electrolytes media.

Medium	c_{CTS}	I_{salt}	A	B	C	R^2
	(mmol kg^{-1})	(mmol kg^{-1})		K^{-1}	K^{-2}	
H_2O	1.026-9.817	0	-65022	373.14	-0.5354	0.9984
H_2O + NaCl	2.880-3.210	9.378-497.0	-4794.3	28.408	-0.0421	0.9464
H_2O + NaOAc	2.916-3.155	11.09-239.6	-2187.2	13.21	-0.02	0.9464
H_2O + NaBenz	2.896-3.557	10.32-245.0	-2177.9	12.089	-0.0168	0.9673
H_2O + NaSal	3.004-3.434	10.32-139.3	-732.16	3.9268	-0.0053	0.9792
H_2O + Na_2SO_4	2.843-3.416	30.11-601.2	-1829.5	11.023	-0.0167	0.9724

observed ΔG_c^0 values in the TX-100 + CTS drug mixed system in the attendance of electrolytes and hydrotropic salts were much lower than those found with pure water medium. The trends in non-spontaneity of clouding was found to be reduced at the higher concentrations of electrolytes and hydrotropes solutions while the concentrations of TX-100 (80.29 mmol kg^{-1}) and CTS drug (3.100 mmol kg^{-1}) were kept constant and followed the order: $\Delta G^o_{c(\text{aq. NaSal})} > \Delta G^o_{c(\text{aq. NaBenz})} > \Delta G^o_{c(\text{aq. } Na_2SO_4)} > \Delta G^o_{c(\text{aq. NaOAC})} > \Delta G^o_{c(\text{aq. NaCl})}$.

Table 12. The magnitudes of various thermodynamic parameters (ΔG_c^0, ΔH_c^0, ΔS_c^0) determined at clouding of the aqueous mixtures of TX-100 (80 mmol kg^{-1}) and CTS in attendance of different electrolytes.

Medium	c_{CTS}	I_{salt}	X_s (×10^4)	ΔG_c^0	ΔH_c^0 (×10^{-2})	ΔS_c^0 (×10^{-2})
	(mmol kg^{-1})	(mmol kg^{-1})		(kJ mol^{-1})	(kJ mol^{-1})	(J mol^{-1} K^{-1})
H_2O	1.026	0	0.1847	31.39	22.45	63.90
	3.004	0	0.5406	28.34	16.98	48.13
	6.655	0	1.197	26.09	10.05	28.18
	9.817	0	1.766	25.00	5.588	15.34
H_2O + NaCl	2.937	9.378	1.687	25.01	-7.424	-22.16
	3.100	20.10	3.616	22.80	-7.189	-21.44
	3.210	35.66	6.411	21.11	-6.576	-19.66
	2.930	78.36	14.08	18.80	-5.866	-17.58
	2.880	100.2	18.00	18.07	-5.435	-16.33
	3.082	141.1	25.33	17.02	-4.135	-12.57
	3.086	176.6	31.67	16.36	-3.630	-11.10
	3.036	250.5	44.87	15.29	-2.156	-6.788
	2.974	497.0	88.63	13.19	1.331	3.572
H_2O + NaOAc	2.916	11.09	1.995	24.45	-5.925	-17.87
	3.095	20.21	3.635	22.60	-5.083	-15.47
	3.087	37.27	6.702	20.84	-4.999	-15.18
	3.163	72.57	13.04	18.82	-4.085	-12.54
	3.059	94.74	17.02	18.07	-4.085	-12.52
	3.155	141.0	25.30	16.92	-3.911	-11.99
	2.985	179.0	32.11	16.19	-3.384	-10.46
	3.117	239.6	42.93	15.31	-2.835	-8.849

Table 12 (Continued).

Medium	c_{CTS} (mmol kg^{-1})	I_{salt} (mmol kg^{-1})	X_s (×10^4)	ΔG_c^0 (kJ mol^{-1})	ΔH_c^0 (×10^{-2}) (kJ mol^{-1})	ΔS_c^0 (×10^{-2}) (J mol^{-1} K^{-1})
H_2O + NaBenz	3.168	10.32	1.856	24.74	4.512	12.31
	3.557	20.88	3.755	22.79	4.139	11.25
	3.399	37.47	6.737	21.17	3.760	10.17
	3.071	73.32	13.18	19.29	3.383	9.117
	3.347	94.80	17.03	18.69	2.506	6.578
	2.896	139.3	25.00	17.66	1.866	4.767
	3.375	177.5	31.83	17.09	0.8358	1.860
	3.399	245.0	43.90	16.31	-0.5592	-1.999
H_2O + NaSal	3.004	9.744	1.753	25.05	2.364	25.85
	3.204	20.47	3.683	23.00	2.225	25.44
	3.210	34.42	6.189	21.70	1.889	21.44
	3.434	74.12	13.32	19.82	1.180	12.33
	3.012	102.0	18.31	18.98	0.9624	9.781
	3.197	139.4	25.03	18.29	0.3807	2.447
H_2O + Na_2SO_4	2.968	30.11	1.805	24.65	-4.600	-14.09
	3.416	60.14	3.606	22.55	-3.940	-12.17
	3.017	104.6	6.267	20.93	-3.654	-11.32
	2.843	175.8	10.54	19.39	-3.294	-10.25
	3.096	243.3	14.57	18.39	-2.728	-8.601
	2.889	294.8	17.65	17.74	-2.043	-6.597
	2.940	402.0	24.05	16.75	-1.270	-4.301
	3.387	601.2	35.93	15.41	0.2123	0.1767

Determination of ΔH_c^0 and ΔS_c^0 in the TX-100 + CTS mixtures in pure water medium showed the positive number as well. However, the magnitudes of both ΔH_c^0 and ΔS_c^0 have been declined with growing of the concentrations of CTS drug while the quantity of TX-100 (80.29 mmol kg^{-1}) was remained unchanged or fixed in the system. For the

clouding of TX-100 and sodium alginate mixture in aq. solutions of NaCl, Na_2SO_4 and Na_3PO_4, the negative values of ΔH_c^0 and ΔS_c^0 were reported in earlier [63]. The magnitudes of the negative values of ΔH_c^0 and ΔS_c^0 were achieved to be reduced with the growing concentrations of salts used. The magnitudes of ΔH_c^0 and ΔS_c^0 depend on the principle of computing the parameters [68]. In a previous study, our research group found the relatively larger magnitudes of ΔH_c^0 and ΔS_c^0 in the drug and nonionic surfactant mixture with the applications of equations 2.11, 2.12 and 2.14 [68]. The appearances of the positive integers for ΔH_c^0 and ΔS_c^0 were highly related to the occurrences of hydrophobic interactions between TX-100 and CTS drug species [82].

However, the calculated values of ΔH_c^0 and ΔS_c^0 obtained from TX-100 +CTS drug system mixed with aquatic electrolytes and hydrotropic salts were found to be negative except at the attendance of relatively higher percentage of NaCl and Na_2SO_4 as well as the hydrotropic salts such as NaSal and NaBenz respectively. The ΔH_c^0 values reveal that the colouding process was endothermic in water and aq. solutions of NaBenz and NaSal solutions while the process became exothermic in nature in aq. solutions of electrolytes (NaCl, NaOAc and Na_2SO_4). Negative ΔH_c^0 and ΔS_c^0 could be appeared in different surfactant-drug mixed systems as observed from the results of several previous studies reported in literatures [57, 83-84]. Rahman *et al.* [59] stated the negative magnitudes of ΔH_c^0 and ΔS_c^0 obtained from the TX-100 + ceftriaxone sodium trihydrate (CFT) mixtures in the presence of some inorganic salts. Akhlaqur *et al.* [84] showed the negative values for both ΔH_c^0 and ΔS_c^0 calculated in the Tw-80 system in the presence or absence of Amikacin sulfate drug with different additives. Rub *et al.* [65] observed the consecutive positive values of ΔH_c^0 and ΔS_c^0 from the interactions of promazine hydrochloride with anionic hydrotropes. Similar variations in the magnitudes of ΔH_c^0 and ΔS_c^0 were observed for TX-100 and MNH drug mixtures in attendance of anionic hydrotropes (NaSal and NaBenz) [68]. The appearance of negative ΔH_c^0 in the surfactant-drug mixtures suggesting the exothermic nature of clouding process in the TX-100 + CTS drug system with aquatic electrolytes and hydrotropic salts additives. However, this exothermic behavior of clouding was gradually changed with the enhancement of electrolyte concentrations and finally turned into an endothermic process which was evidenced from the appearance of positive ΔH_c^0 from the respective mixtures with relatively higher concentrations of NaCl and Na_2SO_4 and hydrotropic salts respectively. The positive magnitudes of

ΔH_c^0 obtained from the studied surfactant-drug mixtures suggest the presence of hydrophobic interaction whereas the negative ΔH_c^0 corresponds to hydrogen bonding and electrostatic interactions. The hydration was likely to be occurred with hydrophilic part of surfactant TX-100 monomer and on the other hand the hydrophobic moiety of the amphiphilic monomer contributed to break the 3D structures of water molecules. Both factors might have contributed to assessment of ΔH_c^0 in the respective TX-100 + CTS mixtures with various additives [27, 77, 85-88]. The degree of ΔH_c^0 could also be affected from the existence of London dispersion forces which were predominantly developed due to the aggregation of micelles in the corresponding surfactant-drug-additives mixed systems [57, 76].

3.2.6.2. Thermodynamic parameters of TX-100 and CTS drug mixture in aqueous potassium salts media

The plot of lnX_s vs. T (CP) showed the non-linear relationship for the studied surfactant-drug system in aq. K-salts media (Figure 31). The A, B, and C values determined for the TX-100 + CTS drug mixture in aq. K-salts media have been presented in Tables 13. Table 14. exposes the values of ΔG_c^0, ΔH_c^0 and ΔS_c^0, for the employed NIS + CTS mixture in various potassium salts media. In all of the studied media, the ΔG_c^0 values were positive for the study system, which shows that the phase separation approach was not spontaneous. The $+\Delta G_c^0$ values progressively diminished as salt content increased, indicating a gradual decrease in the extent of non-spontaneity of cloudy creation of TX-100 solution. With an increase in electrolyte content, the ion-dipole interaction between H_2O and electrolyte upsurges, which augments the salting out of employed NIS from the solution and directs a simple phase separation by improving hydrophobic interaction. The ΔH_c^0 and ΔS_c^0 values for the employed system in aq. KCl, K_2SO_4, $KBrO_3$ and K_3PO_4 solutions were obtained to be negative; which suffer a reduction in the negative values of respective variables. Therefore, the clouding of currently employed system was exothermic in behavior. On the other hand, positive ΔH_c^0 and ΔS_c^0 values were obtained in aq. KI solution and thus the phase partitioning of investigating system is endothermic in aq. KI solution. At nearly 100 mmol kg^{-1} ionic strength of the employed salts solutions, the value of ΔH_c^0 and ΔS_c^0 for different salts show the trend: $\Delta H_c^0[K_2SO_4] < \Delta H_c^0$ $[K_3PO_4] < \Delta H_c^0$ $[KCl] < \Delta H_c^0$ $[KBrO_3] < \Delta H_c^0$ [KI] and ΔS_c^0 $[K_2SO_4] < \Delta S_c^0$ $[K_3PO_4] < \Delta S_c^0$ $[KBrO_3] < \Delta S_c^0$ $[KCl] < \Delta S_c^0$ [KI].

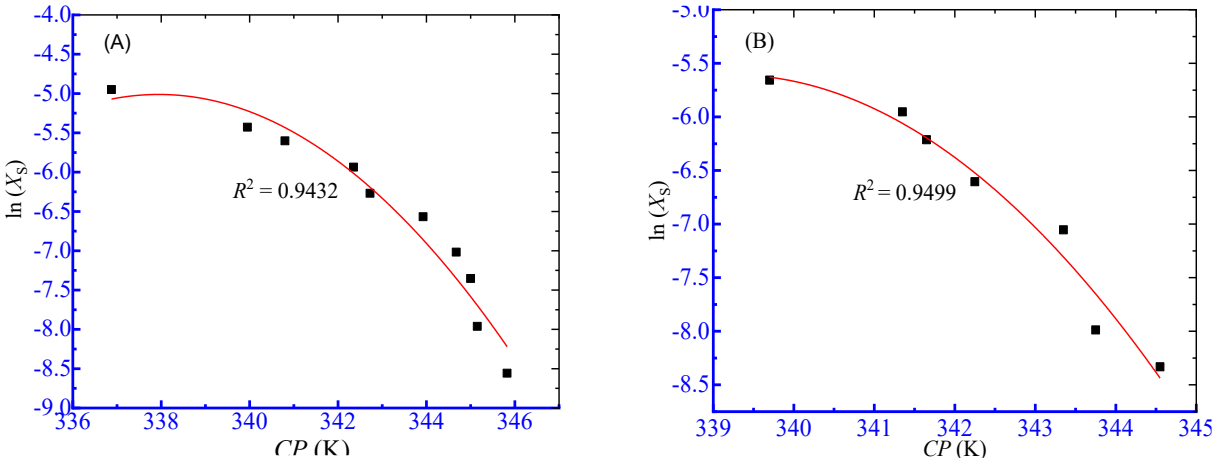


Fig. 31. lnX_s versus CP plot for the clouding of TX-100 and CTS system in (A) H_2O + $KBrO_3$ and (B) H_2O + KCl.

Table 13. The values of A, B and C achieved from the lnX_s verses CP plot for the phase separation of TX-100 (80 mmol kg^{-1}) + CTS drug (3 mmol kg^{-1}) mixture in electrolytes media.

Medium	I_{salt}	A	B	C	R^2
	(mmol kg^{-1})		K^{-1}	K^{-2}	
H_2O + KCl	13.38-194.7	-11435	67.388	-0.0993	0.9666
H_2O + K_3PO_4	59.95-2355	-1253.1	7.6005	-0.0116	0.9557
H_2O + $KBrO_3$	10.68-396.6	-5902.1	34.9	-0.0516	0.9558
H_2O + K_2SO_4	31.47-1195	-569.69	3.519	-0.0055	0.9708
H_2O + KI	7.125-413.4	-6072.2	34.062	-0.0478	0.9785

The negative and positive values of ΔH_c^0 and ΔS_c^0 for the TX-100 + CTS system specify the occurrence of forces which may possibly be hydrophobic and electrostatic in origin. Nevertheless, the $-\Delta H_c^0$ and $-\Delta S_c^0$ disclose the survival of H-bonding and dipole-dipole interaction amongst employed components. The extent of exothermic type forces has the tendency to decrease with enhancing [salts contents] while the impact of hydrophobic forces tends to advance with growing salts contents. But in case of aq. KI medium, the $+\Delta H_c^0$ and $+\Delta S_c^0$ disclose the existence of mainly hydrophobic interaction

amongst the study components. The probable interaction forces between TX-100 and CTS drug in K-based employed salts media are disclosed in Figure 27.

Table 14. The thermodynamic parameters of TX-100 (80 mmol kg^{-1}) + CTS (3 mmol kg^{-1}) mixture in the attendance of electrolytes.

Medium	I_{salt} (mmol kg^{-1})	X_S ($\times 10^4$)	ΔG^0_c (kJ mol^{-1})	ΔH^0_c ($\times 10^{-2}$) (kJ mol^{-1})	ΔS^0_c ($\times 10^{-2}$) (J mol^{-1} K^{-1})
H_2O + KCl	13.38	2.025	23.87	-10.26	-30.47
	18.87	3.526	22.83	-8.653	-25.84
	48.07	9.010	20.14	-7.854	-23.46
	75.31	13.35	18.80	-5.676	-17.13
	111.5	13.77	17.65	-4.500	-13.69
	144.7	18.78	16.90	-3.915	-11.96
	194.7	26.77	15.98	-0.7332	-2.629
H_2O +K_3PO_4	59.95	0.1797	24.76	-4.069	-12.50
	119.0	0.3567	22.70	-3.742	-11.54
	206.9	0.6199	21.09	-3.617	-11.14
	306.3	0.9177	19.93	-3.419	-10.56
	469.2	1.405	18.62	-3.028	-9.423
	647.5	1.938	17.61	-2.531	-7.985
	894.4	2.675	16.67	-2.378	-7.520
	1220	3.645	15.62	-1.516	-4.996
	1512	4.514	14.92	-0.983	-3.408
	2355	7.012	13.40	0.546	1.269
H_2O + $KBrO_3$	10.68	1.922	24.60	-7.847	-23.40
	19.40	3.490	22.84	-7.126	-21.31
	35.63	6.406	21.09	-6.967	-20.80
	49.82	8.957	20.11	-6.622	-19.80
	78.20	14.05	18.78	-5.832	-17.50
	105.5	18.95	17.86	-4.582	-13.89
	147.2	26.42	16.90	-4.195	-12.75
	206.0	36.93	15.87	-2.613	-8.132
	245.1	43.91	15.34	-1.757	-5.619
	396.6	70.86	13.86	1.269	3.356

Table 14 (Continued).

Medium	I_{salt}	X_S (×10^4)	ΔG^0_c	ΔH^0_c (×10^{-2})	ΔS^0_c (×10^{-2})
	(mmol kg^{-1})		(kJ mol^{-1})	(kJ mol^{-1})	(J mol^{-1} K^{-1})
H_2O +K_2SO_4	31.47	0.1887	24.61	-2.759	-8.706
	59.53	0.3569	22.71	-2.629	-8.298
	106.6	0.6390	20.93	-2.393	-7.604
	150.1	0.8993	19.90	-2.273	-7.243
	222.4	1.332	18.69	-2.065	-6.633
	312.8	1.872	17.57	-1.724	-5.644
	439.9	2.631	16.51	-1.479	-4.918
	603.4	3.606	15.47	-1.085	-3.747
	744.7	4.447	14.71	-0.663	-2.479
	1195	7.115	13.03	0.274	0.4537
H_2O + KI	7.125	0.1282	25.76	10.02	28.24
	20.12	0.3619	22.88	8.603	24.11
	36.20	0.6509	21.22	8.124	22.74
	48.68	0.8751	20.39	7.780	21.76
	110.2	1.979	18.05	7.342	20.54
	147.6	2.649	17.23	6.809	19.00
	196.6	3.524	16.44	5.990	16.64
	247.4	4.432	15.79	5.731	15.90
	413.4	7.384	14.35	4.615	12.72

3.2.6.3. Thermodynamic parameters of TX-100 and CTS drug mixture aqueous ammonium salts media

The plot of lnX_s vs. T (CP) exhibited the non-linear relationship for the investigated surfactant-drug system in aq. ammonium salts media (Figure 32). The A, B, and C values determined for the TX-100 + CTS drug mixture in aq. ammonium salts media have been presented in Tables 15. Tables 16 expose the values of ΔG_c^0, ΔH_c^0 and ΔS_c^0, for the employed NIS + CTS mixture in aq. ammonium salts media. Tables 16. present

the typical values of ΔG_c^0, ΔH_c^0 and ΔS_c^0 for the TX-100 + CTS combination in various ammonium salt systems. In every medium under investigation, the values of ΔG_c^0 in the clouding behaviour of the TX-100 + CTS were acquired to be positive, indicating that the separation of phases process was not spontaneous. The $+\Delta G_c^0$ readings in aqueous medium decreased as the amount of CTS medication increased. As the amount of salt in the solution increased, the $+\Delta G_c^0$ values steadily declined, indicating a steady

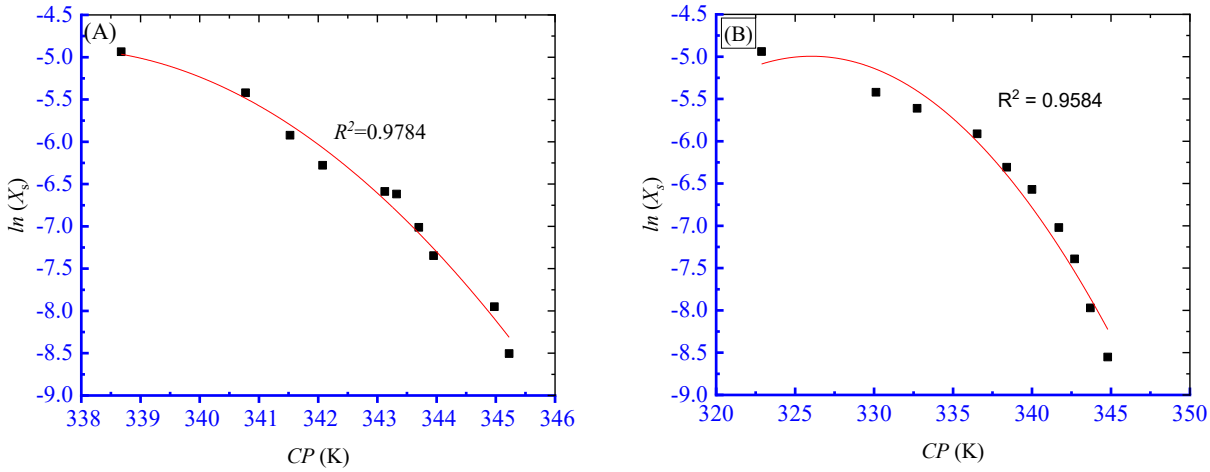


Fig. 32. ln X_s versus CP plot for the phase separation of aq. mixture of TX-100 and CTS in (A) H_2O + NH_4Cl and (B) H_2O + $(NH_4)_2SO_4$ media.

Table 15. The values of A, B and C achieved from the lnX_s verses CP plot for the phase separation of TX-100 (80 mmol kg^{-1}) + CTS drug (3 mmol kg^{-1}) mixture in electrolytes media.

Medium	I_{salt} (mmol kg^{-1})	A	B K^{-1}	C K^{-2}	R^2
H_2O + AmCl	11.25-402.1	-6730	39.84	-0.0590	0.9832
H_2O + AmHP	28.91-1195	-964.0	5.890	-0.0090	0.9511
H_2O + AmSul	32.24-1203	-981.1	5.987	-0.0092	0.9677
H_2O + AmFSul	0.1039-7.022	101999	-589.3	0.8511	0.9263

reduction in the non-spontaneity in the surfactant TX-100 system. Therefore, by raising the concentration of electrolytes, overall non-spontaneity of clouding is reduced. The clouding phase of the TX-100 + CTS mixture in an aqueous medium was characterized by negative values of ΔH_c^0 and ΔS_c^0. As a result, the TX-100 + CTS mixture's clouding process exhibited exothermic behavior, with enthalpy playing a

major role. At lower concentrations, the values of ΔH_c^0 and ΔS_c^0 in the TX-100 + CTS combination in

Table 16. The thermodynamic parameters of TX-100 (80 mmol kg^{-1}) + CTS (3 mmol kg^{-1}) mixture in the attendance of electrolytes.

Medium	I_{salt}	X_S ($\times 10^4$)	ΔG^0_c	ΔH^0_c ($\times 10^{-2}$)	ΔS^0_c ($\times 10^{-2}$)
	(mmol kg^{-1})		(kJ mol^{-1})	(kJ mol^{-1})	(J mol^{-1} K^{-1})
H_2O + AmCl	11.26	2.025	24.41	-8.933	-26.58
	19.60	3.526	22.80	-8.628	-25.67
	35.86	6.448	21.01	-7.388	-22.09
	50.12	9.010	20.04	-7.087	-21.20
	74.32	13.35	18.89	-6.638	-19.88
	76.63	13.77	18.79	-6.399	-19.20
	104.6	18.78	17.85	-5.155	-15.59
	149.2	26.77	16.82	-4.509	-13.69
	246.9	44.22	15.36	-3.635	-11.12
	402.1	71.83	13.90	-1.227	-4.033
H_2O + AmHP	28.91	1.734	24.81	-3.077	-9.653
	61.09	3.663	22.61	-2.931	-9.185
	104.2	6.246	21.02	-2.710	-8.523
	152.4	9.135	19.88	-2.519	-7.957
	227.7	13.64	18.65	-2.214	-7.061
	312.4	18.70	17.69	-1.965	-6.325
	450.8	26.97	16.55	-1.589	-5.214
	599.5	35.83	15.58	-0.9153	-3.219
	751.5	44.87	14.82	-0.4026	-1.671
	1195	71.15	13.22	0.8705	2.296

Table 16 (Continued).

Medium	I_{salt} (mmol kg^{-1})	X_S (×10^4)	ΔG^0_c (kJ mol^{-1})	ΔH^0_c (×10^{-2}) (kJ mol^{-1})	ΔS^0_c (×10^{-2}) (J mol^{-1} K^{-1})
H_2O + AmSul	32.24	1.933	24.51	-3.532	-10.95
	57.59	3.453	22.78	-3.311	-10.29
	102.9	6.166	21.06	-3.112	-9.694
	149.0	8.928	19.95	-2.915	-9.114
	234.2	14.03	18.57	-2.585	-8.150
	304.3	18.22	17.75	-2.281	-7.264
	452.0	27.04	16.54	-1.931	-6.229
	612.1	36.58	15.52	-1.244	-4.205
	741.1	44.25	14.88	-0.7910	-2.847
	1203	71.63	13.26	0.3996	0.8269
H_2O +AmFSul	0.7271	0.0187	37.91	-8.961	-27.02
	3.213	0.0826	33.57	-20.30	-59.80
	3.430	0.0882	33.36	-23.64	-69.52
	6.964	0.1790	31.29	-31.54	-92.52
	49.15	1.263	25.68	-36.10	-105.7

aq. NH_4Cl, $(NH_4)_2SO_4$, and $(NH_4)_2HPO_4$ media seemed negative. It was observed that the negative values of ΔH_c^0 and ΔS_c^0 gradually declined as the concentration of electrolyte increased. Ultimately, the positive values of ΔH_c^0 and ΔS_c^0 were reached at greater concentrations in some cases. The trend is shown by the values of ΔH_c^0 and ΔS_c^0 for various salts at 10 mmol kg^{-1} ionic strength ΔH_c^0 [(NH_4Cl))] < ΔH_c^0 [$(NH_4)_2HPO_4$)] < ΔH_c^0[$(NH_4)_2SO_4$] and ΔS_c^0 (NH_4Cl) <ΔS_c^0 [$(NH_4)_2HPO_4$)] < ΔS_c^0 [$(NH_4)_2SO_4$]. The values of $-\Delta H_c^0$ and $-\Delta S_c^0$ reveal that the primary contact forces between CTS and TX-100 are exothermic, encompassing dipole-dipole, hydrogen bonding, and ion-dipole interactions. However, the exothermic forces tend to diminish as the amount of salts increases.

3.2.6.4. Thermodynamic parameters of TX-100 and CTS drug mixture aqueous nonionic hydrotropes media

The plots of lnX_s vs. T (CP) displayed the non-linear relationship for the investigated surfactant-drug system in aq. NIHDTs media (Figure 33). The A, B, and C values determined for the TX-100 + CTS drug mixture in aq. NIHDTs media have been presented in Tables 17. Tables 18. expose the values of ΔG_c^0, ΔH_c^0 and ΔS_c^0, for the employed NIS + CTS mixture in aq. NIHDTs media.

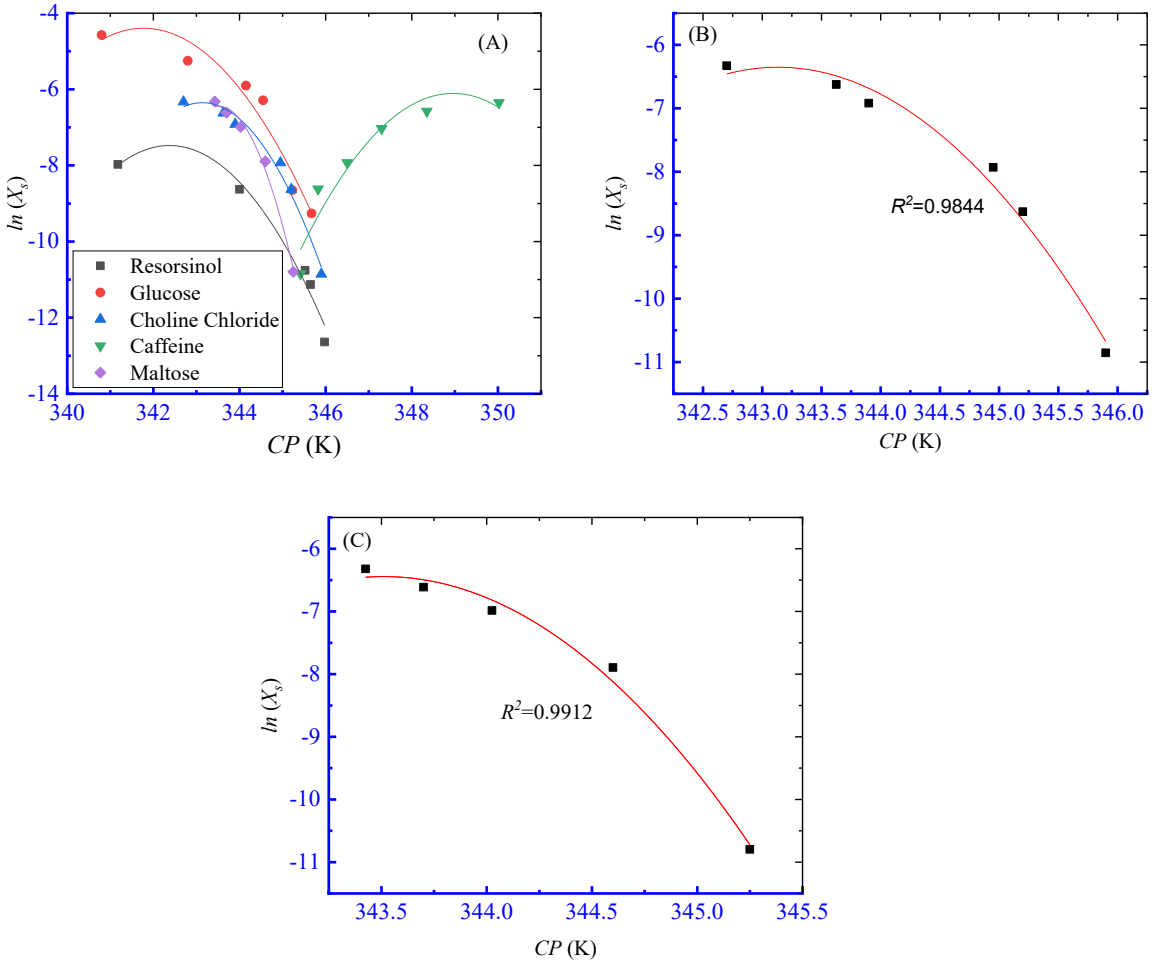


Fig. 33. ln X_s versus CP plot for the phase separation of aq. mixture of TX-100 and CTS in (A) H_2O + Nonionic hydrotropes, (B) H_2O + CCl and (C) H_2O + Maltose media.

Table 17. The values of A, B and C achieved from the lnX_s verses CP plot for the phase separation of TX-100 (80 mmol kg^{-1}) + CTS drug (3 mmol kg^{-1}) mixture in nonionic media.

Medium	C_{hyd}	A	B	C	R^2
	(mmol kg^{-1})		K^{-1}	K^{-2}	
H_2O + Glucose	5.282-579.5	-37273	218.09	-0.319	0.9494
H_2O + Galactose	5.204-599.67	-17167	100.57	-0.1473	0.9918
H_2O + Maltose	1.138-100.11	-166831	971.3	-1.4138	0.9912
H_2O + ChCl	1.073-99.30	-66483	387.47	-0.5646	0.9844
H_2O + Resorsinol	0.1802-3.444	-42719	249.5	-0.364	0.9721
H_2O + Caffeine	1.084-97.13	-39935	228.85	-0.3279	0.9258

Table 18. The thermodynamic parameters of TX-100 (80 mmol kg^{-1}) + CTS (3 mmol kg^{-1}) mixture in the attendance of nonionic hydrotropes.

Medium	$c_{hydrotrope}$	X_S (×10^4)	ΔG^0_c	ΔH^0_c (×10^{-2})	ΔS^0_c (×10^{-2})
	(mmol kg^{-1})		(kJ mol^{-1})	(kJ mol^{-1})	(J mol^{-1} K^{-1})
H_2O + Glucose	5.282	0.9504	26.62	-24.35	-71.20
	9.737	1.752	24.83	-21.44	-62.82
	103.4	18.57	18.02	-17.10	-50.16
	152.5	27.37	16.88	-14.55	-42.77
	292.9	52.43	14.97	-6.022	-18.00
	579.5	103.2	12.96	6.369	18.31
H_2O + Galactose	5.205	0.9364	26.78	-17.418	-50.93
	11.82	2.127	24.38	-15.82	-46.33
	100.6	18.07	18.14	-12.08	-35.49
	150.7	27.04	16.96	-10.41	-30.67
	300.1	53.71	14.95	-7.364	-21.85
	599.7	106.7	12.81	5.581	16.07

Table 18 (Continued).

Medium	$c_{hydrotrope}$ (mmol kg^{-1})	X_S (×10^4)	ΔG^0_c (kJ mol^{-1})	ΔH^0_c (×10^{-2}) (kJ mol^{-1})	ΔS^0_c (×10^{-2}) (J mol^{-1} K^{-1})
H_2O + Maltose	1.138	0.2048	30.99	-48.85	-142.4
	20.71	3.725	22.62	-30.52	-89.21
	51.50	9.258	19.98	-14.42	-42.49
	74.73	13.43	18.90	-5.364	-16.16
	100.1	17.98	18.05	2.270	6.083
H_2O + ChCl	1.073	0.1930	31.22	-31.04	-90.64
	9.938	1.788	24.77	-23.08	-67.58
	20.00	3.598	22.74	-20.26	-59.38
	55.01	9.889	19.78	-8.475	-25.22
	73.84	13.27	18.93	-5.413	-16.30
	99.30	17.84	18.03	4.815	13.52
H_2O + Resorsinol	0.1802	0.0324	36.36	-23.58	-69.22
	0.8142	0.1465	31.99	-21.19	-62.23
	1.183	0.2129	30.90	-20.27	-59.56
	9.967	1.793	24.67	-9.169	-27.37
	19.15	3.444	22.62	10.88	31.24
H_2O + Caffeine	1.084	0.1950	31.15	23.08	65.92
	10.03	1.804	24.78	20.46	58.45
	20.03	3.602	22.84	16.12	45.87
	49.20	8.845	20.30	10.94	30.91
	77.68	13.96	19.04	4.056	11.10
	97.13	17.45	18.48	-7.094	-20.79

The ΔG^0_c values associated with the clouding process were positive (i.e. the process is nonspontaneous). The ΔH^0_c and ΔS^0_c values were negative at lower NIHDT content, then the magnitudes of $-\Delta H^0_c$ and $-\Delta S^0_c$ experienced a decline with the augmentation of NIHDT concentration and attained a positive value at highest NIHDT concentration used with exception of the result obtained in case of aq. caffeine medium. In aq. caffeine medium, the reverse effect was achieved in comparison to other NIHDTs. Therefore,

the clouding of TX-100 + CTS drug mixture is happened exothermically and the main contribution for the occurrence is paid from the enthalpy only at lower concentrations of all NIHDTs except caffeine and the entropy contribution is the driving factor of the happening of cloudy creation in aq. caffeine medium. The negative values of both entropy and enthalpy indicates the existence of hydrogen bonding and electrostatic interactions [89]. These particular trends in ΔH_c^0 and ΔS_c^0 values were also previously noted in the context of nonionic surfactant clouding processes in presence of electrolytes [90]. The negative values of ΔH_c^0 and ΔS_c^0 were obtained by Rub et al. [91-93] for certain amphiphilic medicines when Tween 80 and other additive mixes were present. When more H_2O molecules hydrate in the hydrophilic head part of a surfactant compared to the breaking of H_2O structure surrounding the hydrophobic alkyl chains of the monomers, the resultant negative value of ΔH_c^0 is more likely to be happened [27, 94-95]. The obtained results showed that at the separation of the phases of Triton X-100 in the presence of NIH's, the values of $\Delta G^0{}_c$ were regulated by mutually ΔH_c^0 and ΔS_c^0. Positive ΔH_c^0 values are caused by H_2O structural abnormalities around the hydrophobic alkyl portions of surfactant monomers [96]. Positive values of ΔH_c^0 indicate the destruction of ordered H_2O surrounding the hydrophobic portions of the amphiphiles [29, 97-99], while negative values further highlight the significance of the forces of London dispersion as a drawback of association of the amphiphile system [100-101].

3.2.7. Enthalpy-entropy compensation of clouding phenomena

For the TX-100 + CTS drug mixture in aqueous medium and aqueous solutions of salts and ionic/nonionic hydrotropes media, the enthalpy-entropy compensation of clouding was assessed from the linear plots of ΔH_c^0 vs. ΔS_c^0 with R^2 values in the range of 0.9968-1. Such plots for the working system are sketched in Figs. 34, 35, 36, 37. The magnitudes of T_c and $\Delta H_c^{0,*}$ acquired from the present experiments of clouding are demonstrated in Tables 19a, 19b, 19c and 19d. The parameters $\Delta H_c^{o,*}$ and T_c demonstrate the solute-solute interactions and solute-solvent interactions during the micelle formation in the TX-100 + CTS system in the existence of electrolytes and hydrotropic salts [102-104]. The T_c values in the range from 332.6 to 3357.03 K have been recorded for the clouding of TX-100 + CTS drug in additives media used. The

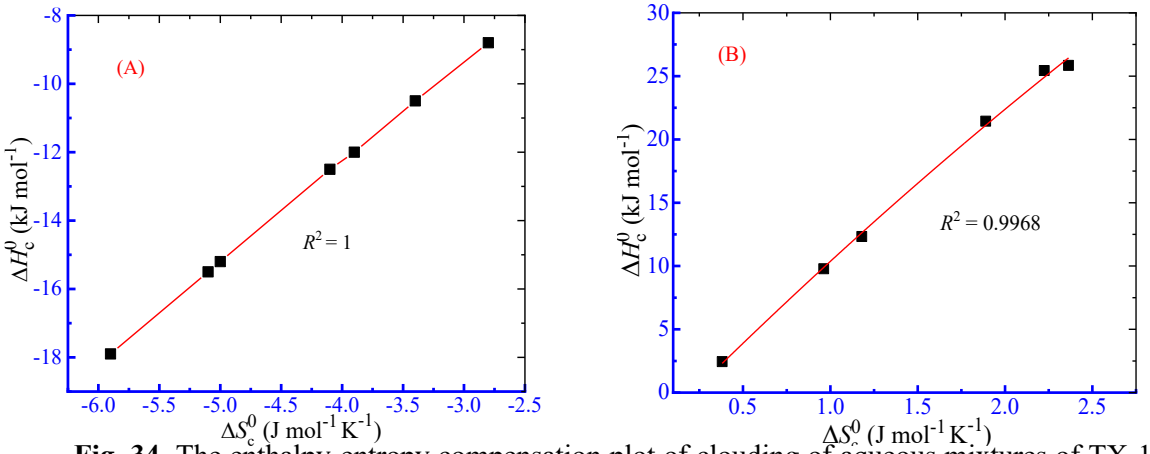


Fig. 34. The enthalpy-entropy compensation plot of clouding of aqueous mixtures of TX-100 and CTS in (A) H_2O + CH_3COONa and (B) H_2O + NaSal.

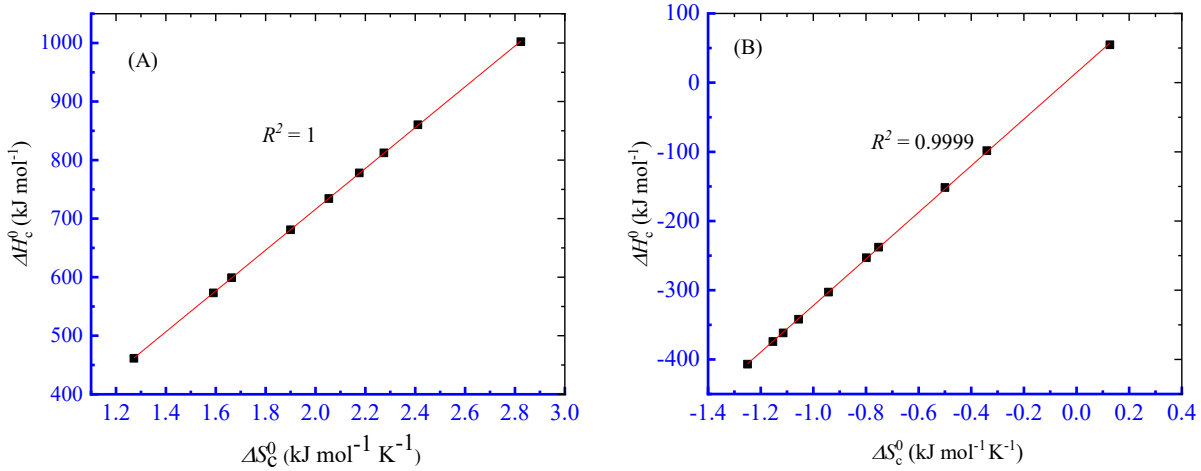


Fig. 35. The enthalpy-entropy compensation plot for the clouding of TX-100 and CTS in (A) H_2O + KI and (B) H_2O + K_3PO_4.

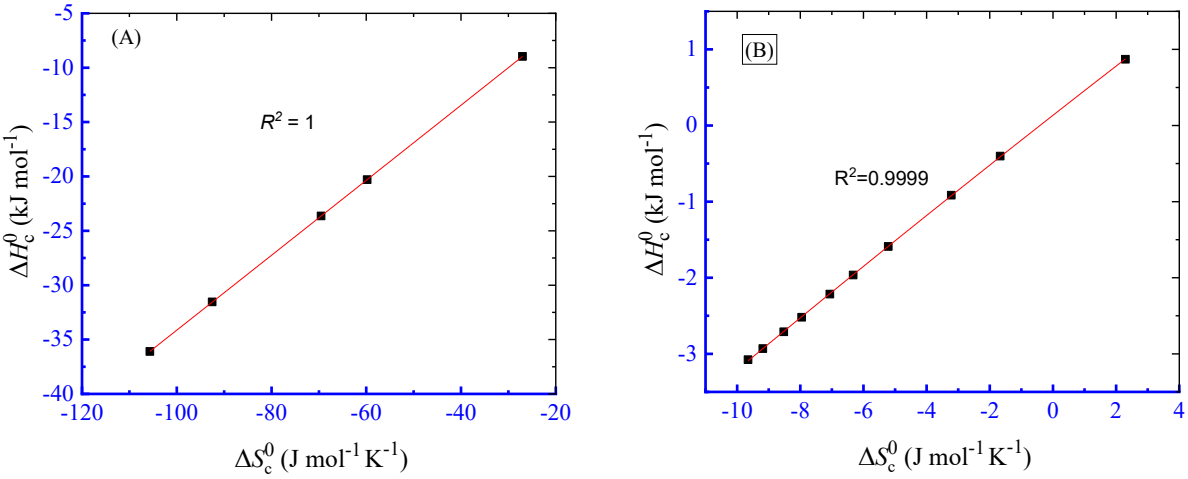


Fig. 36. The enthalpy-entropy compensation plot for the clouding of TX-100 and CTS in (A) H_2O + AmFSul and (B) H_2O + AmHP.

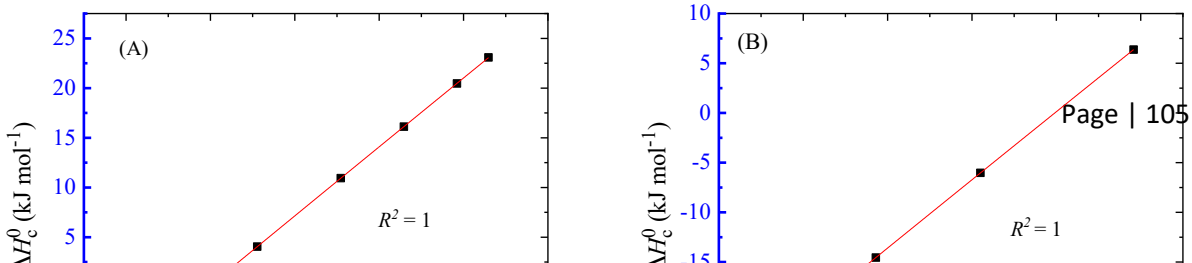


Fig. 37. The enthalpy-entropy compensation plot for the clouding of TX-100 and CTS in (A) H_2O + Caffein and (B) H_2O + Glucose.

Table 19a. The extents of $\Delta H_c^{o,*}$, T_c and R^2 at the clouding of the aqueous mixtures of TX-100 (80 mmol kg^{-1}) and CTS (3 mmol kg^{-1}) in electrolytes media.

Medium	I_{salt}	$\Delta H_c^{o,*}$	T_c	R^2
	(mmol kg^{-1})	kJ mol^{-1}	K	
H_2O[a]	0	26.67	347.16	1
H_2O + NaCl	9.378-497.0	13.71	341.1	1
H_2O + NaOAc	11.09-239.6	19.13	341.75	1
H_2O+ NaBenz	10.32-245.0	16.70	353.4	1
H_2O + NaSal	9.744-139.4	19.69	357.03	0.9999
H_2O+ Na_2SO_4	30.11-601.2	17.05	337.74	0.9999

Table 19b. The $\Delta H_c^{0,*}$, T_c and R^2 for the clouding of TX-100 (80 mmol kg^{-1}) + CTS (3 mmol kg^{-1}) mixture in electrolytes media.

Medium	I_{salt}	$\Delta H_c^{0,*}$	T_c	R^2

	(mmol kg^{-1})	kJ mol^{-1}	K	
H_2O + KCl	13.38-194.7	17.60	342.1	1
H_2O + K_3PO_4	59.95-2355	14.60	336.7	0.9999
H_2O + $KBrO_3$	10.68-396.6	14.74	341.4	1
H_2O + K_2SO_4	31.47-1195	14.82	333.4	0.9998
H_2O + KI	7.125-413.4	18.48	348.8	1

Table 19c. The $\Delta H_c^{0,*}$, T_c and R^2 for the clouding of TX-100 (80 mmol kg^{-1}) + CTS (3 mmol kg^{-1}) mixture in electrolytes media.

Medium	I_{salt}	$\Delta H_c^{0,*}$	T_c	R^2
	(mmol kg^{-1})	kJ mol^{-1}	K	
H_2O + NH_4Cl	11.26-402.10	16.70	342.2	1
H_2O+ $(NH_4)_2HPO_4$	1.734-71.15	13.40	332.6	0.9999
H_2O + $(NH_4)_2SO_4$	1.933-71.63	14.80	335.4	0.9999
H_2O +AmFSul	0.7271-49.15	34.61	344.9	1

Table 19d. The $\Delta H_c^{0,*}$, T_c and R^2 for the clouding of TX-100 (80 mmol kg^{-1}) + CTS (3 mmol kg^{-1}) mixture in electrolytes media.

Medium	$C_{hydrotrope}$	$\Delta H_c^{0,*}$	T_c	R^2
	(mmol kg^{-1})	kJ mol^{-1}	K	
H_2O + Glucose	5.282-579.5	11.454	343.17	1
H_2O + Galactose	5.205-599.7	9.2603	343.2	1
H_2O + Maltose	1.138-100.11	19.482	344.35	1
H_2O + ChCl	1.073-99.30	18.534	344.31	1
H_2O + Resorsinol	0.1802-3.444	17.981	343.21	1
H_2O + Caffeine	1.084-97.13	16.581	347.71	1

calculated T_c values were observed to be varied from of 337 K to 357 K which indicated the existence of hydrophobic interactions between the hydrophobic structural moieties of TX-100 and CTS drug species. In a previous study conducted by S. Mahbub (2020) reported the T_c values for the phase separation of pureTX-100 which were in the range

of 323 to 335 K in the electrolyte media and 341.47 K in the hydrotrope urea media [105]. These interesting results of T_c were close to the data (270-330 K) obtained from the studies in the fluids of living cells and may find potential applications in the evaluation of water contents in various in protein solutions [106]. Lumry and Rajender [5] previously stated the T_c between 250 and 350 K by assessing the aq. proteins and low molecular weight solutes. They also informed that the T_c values of 250 to 350 K range might be applied for identifying the appearance of H_2O in protein solution. The previously stated T_c values for the phase partitioning of TX-100 and antidiabetic drug mixture in aq. potassium salts solutions have the similarity to the result achieved in the present case [105]. Therefore, the current employed systems demonstrate the comparable behavior with biological systems. The entropy-enthalpy compensating phenomenon for numerous similar systems involving surfactants have been illustrated in the literature [107-108]. However, all calculated $\Delta H_c^{0,*}$ values for the TX-100 + CTS mixture were acquired to be positive. It is reported that the $\Delta H_c^{0,*}$ values demonstrate the solute-solute interactions and the $-\Delta H_c^{0,*}$ values are characteristics of micellar stability [107-109]. The $+\Delta H_c^{0,*}$ values have also been reported by us and other researchers for the cloudy formation of nonionic amphiphiles [107-109]. The T_c concentrations discovered in the TX-100 + MNH systems with aqueous ammonium-salt media from the current study were quite similar to the data previously published in the literature [105], indicating that the systems under study are comparable to biological systems. These findings demonstrated that entropy and enthalpy are mutually reinforcing, and that the mixture of surfactant and CTS in the presence of nonionic hydrotropes are significantly enriched with the solute-solvent interaction.

3.3. Binding study of drug with surfactant

3.3.1. Analysis of the Absorption spectra of TX-100, CTS drug and their mixture

Using UV visible spectroscopy, the binding behavior of the BSA protein with TX-100 was investigated. Through the use of UV-visible spectroscopy, the maximum wavelength of pure TX-100 was found at approximately 276 nm, which is comparable

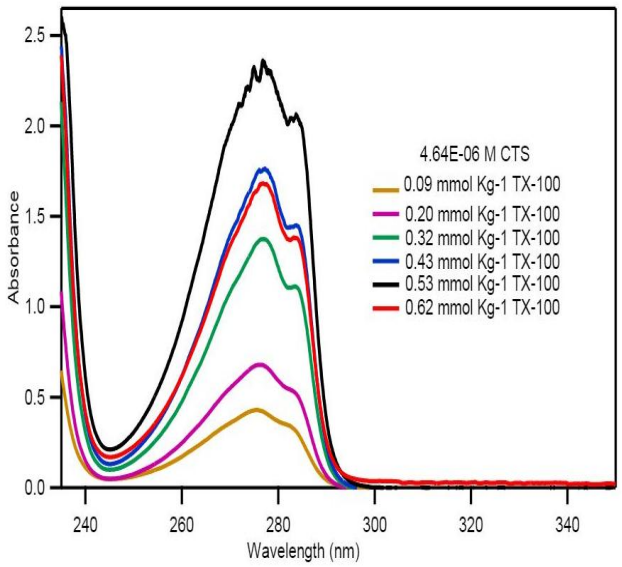


Fig. 38. Absorption Verses wavelength diagram for CTS + TX-100 in aqueous solution

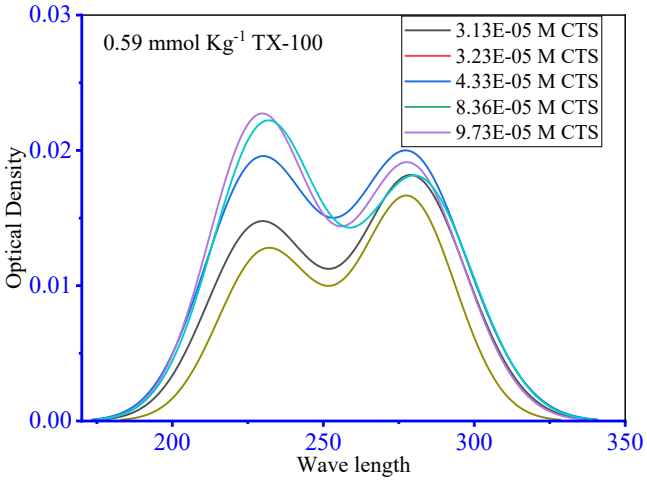


Fig. 39. Optical Density verses wavelength diagram for TX-100 + CTS in aqueous solution.

to the literature reported value [110]. The UV spectra, obtained for the current investigation at 298.15K, are shown in Figures 38 and 39. When TX-100 is present, the λ max values of pure CTS drugs increase, indicating that the presence of interaction between CTS and TX-100. The *CMC* value of TX-100 in water was reported to be 0.33 Mm [111]. In the current study, the *CMC* was determined for the TX-100 in aq. 1.06 ×

10^{-6} mol kg^{-1} CTS drug solution, the measurement was performed from the absorbance vs log[TX-100] plot (Figure 40). The *CMC* value of 0.46 mmol kg^{-1} indicates that the introduction of CTS drug disfavor the micellization of employed NIS, which has been identified by the augmentation of *CMC* value.

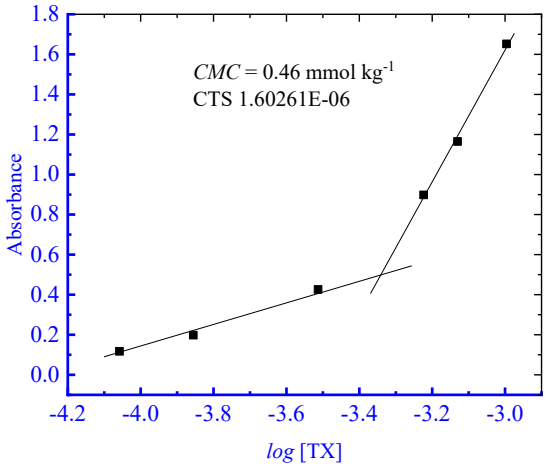


Fig. 40. Absorbance *vs.* log[TX-100] plot for the determination of *CMC*

Because of their minimal *CMC* values, even at very high blood dilution levels, nonionic surfactants are thought to be the greatest options for drug delivery compared to cationic and anionic surfactants. Additionally, they are more physiologically tolerable. because hydrophobic medications dissolve easily in their micellar core. Usually, NISs are employed as medication transporters

3.3.2. Assessment of the binding constant for TX-100 complexation with CTS drug

The Benesi-Hildebrand equation was applied to get the binding constant (K_b) for the drug-surfactant interaction at the maximum wavelength [112]. A typical Benesi-Hildebrand plot (D/A against 1/C) is given in Figure 41. It is a straight line with an intercept of 1/ε and a slope of 1/(εK_b) and consequently, the K_b value was computed from the ration of intercept and slope values. The thermodynamic have been utilized to evaluate thermodynamic parameters based on the temperature dependence of K_b values.

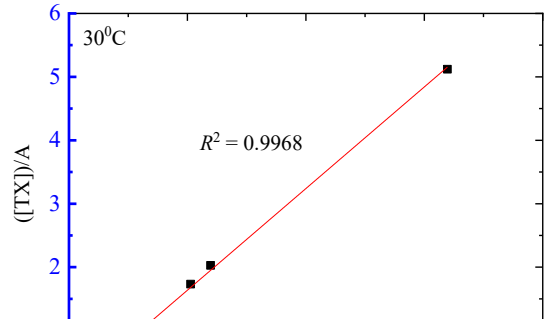


Fig. 41. The Benesi-Hildebrand plot for CTS-TX-100 complex by plotting $\frac{[TX-100]}{A}$ **versus** $\frac{1}{[CTS]}$ at 303.15 K.

Table 20. The K_b and thermodynamic parameters associated with the TX-100 (0.594 mmol kg^{-1}) binding with CTS drug.

T	ln K_b	ΔG_b^o	ΔH_b^o	ΔS_b^o	$\Delta H_c^{o,*}$	T_c	R^2
K		kJ mol^{-1}	kJ mol^{-1}	J mol^{-1} K^{-1}	kJ mol^{-1} K^{-1}	K	
293.15	6.841	-16.67	58.94	257.9	-19.48	303.11	0.9999
298.15	7.155	-17.73	92.74	370.6			
303.15	7.932	-19.99	128.7	490.6			
308.15	8.672	-22.22	167.0	613.9			

Tables 20. gives the values of the binding constant *(K_b),* molar absorptivity (ε) and thermodynamic parameters for the drug-TX-100 system in aqueous solutions at different temperatures at a wavelength of 276 nm. The lnK_b values were observed to with the growth in temperature. In every instance, the values of ΔG_b^o are found to be negative, indicating that the binding process is spontaneous [113-115]. The $-\Delta G_b^o$ values are found to be increased with the escalation of temperature for the binding study of TX-100 with CTS; the findings dictate the upsurge of spontaneity of binding scheme. The ΔH_c^o and ΔS_c^o values are positive for the complexation of TX-100 with CTS which disclose that the binding phenomenon is endothermic in nature and contributed by entropy domination. The binding interactions between CTS and TX-100 are suggested to be mainly hydrophobic and pi-pi interactions [116-122].

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4. Conclusions

The current investigation discloses the micellization, phase separation and binding behaviour of ceftriaxone sodium drug with surfactants in several inorganic () and organic additives (hydrotropes (HDTs)) media. The experiments have been performed using conductivity, cloud point and UV-visible spectroscopic techniques. Using the conductivity technique, several micellar parameters (e.g., CMC, α, and β) for the micellization of a cationic surfactant (CPC) and a CTS drug mixture have been determined. The results demonstrate that these variables (e.g., CMC, α, and β) of micellization is dependent on the concentration of drug, types and concentration of the additives (hydrotropes/ salts/polyols) used, and temperature of the system. The employed electrolytes (NaCl and Na_2SO_4) favour the micelle development of the CPC + CTS system while the HDT imposes the delayed micellization; the effects are augmented with the upsurge of additives concentrations. The CMC values of CPC + CTS mixed systems are decreased (earlier micellization) in aqueous glucose and aq. maltose solution in comparison to water medium while the CMC values are increased (delayed micellization) in aq. galactose solution. The CMC values of the CPC + CTS mixture are dependent on the temperature variation in all the media used. The increase of temperature causes the delayed micellization of CPC + CTS systems in water and aq. solution of NaCl, Na_2SO_4, choline chloride and galactose whereas the micellization becomes favourable (earlier micellization with lesser extent of amphiphile) in aq. solutions of NaBenz, ReSC, caffeine, and glycerol media. Also, reverse CMC vs T plots were detected in aq. glucose and maltose solutions while the opposite trend was found in aq. urea medium. The ΔG_m^0 values of CPC + CTS systems in water and aq. solution of salts/hydrotropes/polyols is negative, indicating that the aggregation of the CPC + CTS mixture happens spontaneously. The ΔH_m^0 values for the micellization of CPC + CTS mixture were negative (exothermic micellization) and positive (endothermic micellization) at lower and higher temperatures respectively in water and aq. solutions of NaCl, urea and glucose whereas the reverse trend was acquired in aq. Na_2SO_4 solution. The micellization of the CPC + CTS mixture was exothermic (the ΔH_m^0 values are negative) in nature in aq. solutions of 4-ABA, galactose, maltose, choline chloride and caffeine, whereas the micellization became endothermic (the ΔH_m^0 values are positive) in behavior aq. solutions of NaBenz, glycerol and resorcinol. The ΔS_m^0 values are positive in water and in aq. solutions of employed salts/HDTs/polyols media except

in aq. glactose and maltose media. In aq. solutions of galactose and maltose media, the ΔS_m^0 values are found to be negative. Therefore, the obtained ΔH^0_m and ΔS^o_{m} values of the micellization of CPC + CTS mixture in additives media indicate that the probable binding forces between CTS and CPC are mainly ion-dipole, dipole-dipole and hydrophobic interactions. The enhanced hydrophobic interaction is achieved in aq. NaBenz, glycerol and ReSC media whereas electrostatic interactions are the dominating forces in aq. galactose and maltose solutions.

The physicochemical and thermodynamic characteristics of the TX-100 + CTS system with various additives were examined with the measurement of CP. The introduction of CTS drug enhanced the CP of aq. solution of TX-100 and the effect was augmented with the concentrations of CTS drug. For the clouding of TX-100 (80 mmol kg^{-1}) + CTS (3 mmol kg^{-1}) drug mixture, the decreasing trend in the magnitudes of CP (solubility of TX-100 + CTS system becomes decreased) was observed with a rise in the concentration of electrolytes, HDT and polyols used herein the present study with a few exceptions. The extents of CP were found to be increased (solubility of TX-100 + CTS system undergoes enhancement) with the augmentation of the concentrations of caffeine, KI, NaBenz and NaSal. The ΔG_c^o values of TX-100 and CTS drug mixture were found to be positive which indicated that the phase separation of the study system in all employed solvents media is nonspontaneous. However, the extent of non-spontaneity of cloudy creation undergoes decline with the enhancement of concentrations of salts/HDTs/polyols used. The ΔH_c^o, and ΔS_c^o values were obtained to be positive for the clouding process of study mixture in water, and aq. solutions of NaBenz, NaSal, KI and caffeine media where the positive values experienced a reduction with the concentrations of CTS drug (in the case of water) and additives (NaBenz, NaSal, KI and caffeine). Thus the clouding process was endothermic and entropy dominated in these solvents. On the other hand, The ΔH_c^o and ΔS_c^o values were attained to be negative for the clouding process of working system in aq. solutions of employed Na/K/ammonium-based salts, nonionic HDTs (resorcinol and choline chloride) and polyols (glucose, galactose and maltose) media. The magnitudes of $-\Delta H_c^o$ and $-\Delta S_c^o$ values were suffered a lessening with the enhancing concentrations of employed Na/K/ammonium based salts, nonionic HDTs (resorcinol and choline chloride) and polyols (glucose, galactose and maltose). Thus the clouding process was

exothermic and enthalpy dominated in these cases. Based on enthalpy and entropy values acquired in the present investigations, the recommended interactions between TX-100 and CTS drug might be hydrophobic and pi-pi interaction in water, and aq. solutions of NaBenz, NaSal, KI and caffeine media whereas in aq. solutions of employed Na/K/ammonium-based salts, nonionic HDTs (resorcinol and choline chloride) and polyols (glucose, galactose and maltose) media, the interaction forces are dipole-dipole, H-bonding, and pi-pi interactions between the components. Using a UV-visible spectroscopic tool, the complexation of TX-100 with CTS drug was performed and the binding constant (K_b) was computed from the Benesi-Hildebrand equation. The values of the binding constant were found to be dependent on the temperature variation. The binding of TX-100 with CTS drug was spontaneous as detected from negative free energy ($\Delta G_{b)}^{o}$ of binding scheme. The positive values of ΔH_b^o and ΔS_b^o indicate that the probable interaction forces are hydrophobic interaction, dipole-dipole forces and pi-pi interactions. The interesting results of this study has provided significant information on properties and nature of interactions between surfactant and drug in their mixtures in the manifestation of additives, which will be highly useful to the future studies on pharmaceutical formulations, drug delivery systems, storage purposes as well as in numerous industrials applications.

DECLARATION OF THE APPLICANT

Details of the Candidate	
Name of the Candidate:	Md. Nazrul Islam
Registration No:	3023
Roll No:	67
Session:	2018-19
Title of Topic:	Physico-chemical study of the interaction of ceftriaxone sodium trihydrate antibiotic drug with surfactants in absence/presence of different additives at different temperatures
Faculty/Institute:	Mathematical & Physical Sciences
Department:	Chemistry
Contact Information:	PhD Researcher, Department of Chemistry, Jahangirnagar University & Assistant Professor, Dhaka Residential Model College, Mohammadpur, Dhaka-1207.
Mobile:	01717111671
E-mail ID (in block letter):	chemnazrul@gmail.com
Details of the Supervisor	
Name of the Supervisor:	Dr. Md. Anamul Hoque
Designation & Address:	Professor, Dept. of Chemistry, Jahangirnagar University, Dhaka-1342, Bangladesh
Mobile:	01911054897
E-mail ID:	ahoque_ju@juniv.edu
Name of the Co- Supervisor:	Dr. Shariff Enamul Kabir
Designation & Address:	UGC Professor, Department of Chemistry, Jagannath University, Dhaka-1100, Bangladesh
Mobile:	01713464698
E-mail ID:	skabir_ju@yahoo.com

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Signature of the Supervisor

Name: Prof. Dr. Md. Anamul Hoque

Signature of the Applicant

Name: Md. Nazrul Islam

DECLARATION OF AUTHORSHIP

Name (in capitals)	: MD. NAZRUL ISLAM
Registration No	: 3023
Roll No	: 67
Department/Institute (in capitals)	: CHEMISTRY/ MATHEMATICAL & PHYSICAL SCIENCES
Supervisor	: Prof. Dr. Md. Anamul Hoque
Co-Supervisor	: Prof. Dr. Shariff Enamul Kabir
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